IMMUNOCONJUGATES TARGETING CD46 AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/062,740, filed August 7, 2020; which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] CD46, also known as CD46 complement regulatory protein, cluster of differentiation 46 and membrane cofactor protein, is an inhibitory complement receptor. Overexpression of CD46 has been observed in several cancers, such as breast cancer, colorectal cancer, liver cancer, lung cancer, or prostate cancer. In some cases, overexpression of CD46 has been characterized as a negative prognostic factor. For example, overexpression of CD46 has been correlated with shorter progression-free time and shorter overall survival time in breast cancer patients and ovarian cancer patients. New therapies and treatment regimens targeting CD46 for the treatment of cancer are needed.

SUMMARY

[0003] The present disclosure provides immunoconjugates for the treatment conditions characterized by cell surface CD46 expression, such as metastatic castration resistant prostate cancer and multiple myeloma.

[0004] [0003][0004] In some embodiments, immunoconjugate is administered to said human subject 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 2.57 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 2.57 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 2.5, or7 mg/kg, about 1.8 to 2.0about 2.5 mg/kg, about 1.8 to about 2.4 mg/kg, or about 1.8 to about 2.0 mg/kg. In some embodiments, the immunoconjugate is administered to said human subject at a dose from about 1.5 to about 2.5 mg/kg. In some embodiments, the immunoconjugate is administered to said human subject 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. In some embodiments, the immunoconjugate is administered to said human subject at a dose of about 1.8, about 2.4, or about 3.2 mg/kg. In some

embodiments, the immunoconjugate is administered to said human subject at a dose of about 1.8 mg/kg. In some embodiments, the immunoconjugate is administered to said human subject at a dose of about 2.4 mg/kg. In some embodiments, the immunoconjugate is administered to said human subject at a dose of about 3.2 mg/kg.

[0005] In some embodiments, the immunoconjugate is administered to said human subject via intravenous infusion. In some embodiments, immunoconjugate is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days. In some embodiments, immunoconjugate is administered to said human subject every 21 days.

[0006] In some embodiments, the 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. In some embodiments, the effector comprises a drug. In some embodiments, the drug is an anti-cancer drug. In some embodiments, the drug is a chemotherapeutic agent. In some embodiments, the drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor. In some embodiments, the drug is a microtubule inhibitor. In some embodiments, the microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative thereof), or maytansine (or a derivative thereof). In some embodiments, the microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF). In some embodiments, the microtubule inhibitor is monomethylauristatin E (MMAE).

[0007] In some embodiments, the ratio of said effector agent to said recombinant antibody is from about 3 to about 5. In some embodiments, the ratio of said effector agent to said recombinant antibody is about 4.

[0008] In some embodiments, effector agent is conjugated to said recombinant antibody via a linker. In some embodiments, the linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule. In some embodiments, the linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB).

[0009] In some embodiments, the cancer is prostate cancer. In some embodiments, the prostate cancer is castration resistant prostate cancer. In some embodiments, the cancer is multiple myeloma. In some embodiments, the multiple myeloma is relapsed or refractory multiple myeloma.

[0010] In some embodiments, the immunoconjugate binds CD46 expressed on the surface of a cell and is internalized into the cell. In some embodiments, the immunoconjugate is internalized into said cell via macropinocytosis.

[0011] In another aspect, the disclosure provides a method of treating cancer in a human subject in need thereof, said method comprising administering to said 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; and (b) monomethylauristatin E (MMAE) that is conjugated to said recombinant antibody via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB) linker; wherein said immunoconjugate is administered at a dose from about 1.0 to about 4.0 mg/kg.

[0012] In another aspect, the disclosure provides pharmaceutical composition that comprises (a) an immunoconjugate at a concentration of about 10.0 ± 5.0 mg/mL, and (b) a histidine buffer; and wherein said 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; and (b) an effector agent that is conjugated to said recombinant antibody.

[0013] In some embodiments, the pharmaceutical composition comprises from about 10 to about 30 mM histidine buffer. In some embodiments, the pharmaceutical composition comprises from about 10 to about 20 mM histidine buffer. In some embodiments, the pharmaceutical composition further comprises cryoprotectant. In some embodiments, the cryoprotectant is a saccharide. In some embodiments, the sucrose or trehalose. In some embodiments, the pharmaceutical composition further comprises a stabilizing agent. In some embodiments, the stabilizing agent prevents denaturation of said recombinant antibody, prevents aggregation of said immunoconjugates, or both. In some embodiments, the stabilizing agent is a polysorbate. In some embodiments, the stabilizing agent is polysorbate 80. In some embodiments, the pharmaceutical composition has a pH from about 5.0 to about 7.0.

[0014] In some embodiments, the stabilizing agent is a polymer. In some embodiments, the polymer is a synthetic or semi-synthetic polymer. The polymer may be a linear polymer such as povidone or polyvinyl alcohol. The polymer may be a copolymer such as PVA-PEG graft

copolymer. The polymer may be Ionic, such as carboxymethylcellulose sodium, sodium alginate, chitosan, or polyethylene glycol. A semisynthetic polymer may be a non-ionic polymer such as HPMC, HPC, or HEC. In some embodiments, the stabilizing agent is a surfactant. The surfactant may be an ionic surfactant such as docusate sodium, sodium lauryl sulfate, or polyethylene imine or a non-ionic surfactant such as Tweens, poloxamers, D-α-tocopheryl, polyethylene glycol succinate, block co-polymers of polyethylene oxide-polyethylene oxide-Polyethylene oxide. In some embodiments, the stabilizing agent is food proteins, amino acids, or co-polymers. In some embodiments, the stabilizing agent is Captisol, Monosteol, Microcrystallin cellulose and corboxymethylcellulose, sorbitol, or a cellulose gel.

[0015] In some embodiments, the pharmaceutical composition comprises a buffering agent. The buffering agent may be selected from acetate, citrate, tartrate, histidine, glutamate, phosphate, Tris, glycine, bicarbonate, succinate, sulfate, or nitrate. In some embodiments, the pharmaceutical composition comprises a tonicity modifier. The tonicity modifier may be selected from mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, potassium chloride, glycerol, and glycerin. In some embodiments, the pharmaceutical composition comprises a bulking agent. The bulking agent may be a sugar or polyol selected from surcrose, trehelose glucose, lactose, sorbitol, mannitol, and glycerol. The bulking agent may be an amino acid slected from arginine, aspartic acid, glutamic acid, lysine, proline, glycine, histidine, methionine, and alanine. The bulking agent may be a polymer or protein selected from gelatin, PVP, PLGA, PEG, dextran, cyclodextrin and derivatives, starch derivatives, HSA and BSA. In some embodiments, the pharmaceutical composition comprises an antioxidant. The antioxidant may be selected from histamine, methionine, ascorbic acid, glutathione, vitamin E, or poly(ethylenimine). In some embodiments, the pharmaceutical composition comprises an antimicrobial preservative. The pharmaceutical preservative may be selected from benzyl alcohol, metacresol, phenol, and 2-phenoxyethanol. In some embodiments, the pharmaceutical composition may comprise a chelating and/or complexing agent. The chelating agent may be edetate disodium, diethylenetriamine pentaacetic acid, citric acid, hexaphosphate, thioglycolic acid, or zinc.

[0016] In some embodiments, the 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. In some embodiments, the effector comprises a drug. In some embodiments, the drug is an anti-cancer drug. In some embodiments, the drug is a chemotherapeutic agent. In some embodiments, the drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor. In some embodiments, the drug is a microtubule inhibitor. In some embodiments, the microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative thereof), or maytansine (or

a derivative thereof). In some embodiments, the microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF). In some embodiments, the microtubule inhibitor is monomethylauristatin E (MMAE). In some embodiments, a ratio of said effector agent to said recombinant antibody in said population of immunoconjugates is from about 3 to about 5. In some embodiments, the ratio of said effector agent to said recombinant antibody in said population of immunoconjugates is about 4.

[0017] In some embodiments, the said effector agent is conjugated to said recombinant antibody via a linker. In some embodiments, the linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule. In some embodiments, the linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB).

[0018] In another aspect, the disclosure provides, 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; (b) monomethylauristatin E (MMAE) that is conjugated to said recombinant antibody via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB) linker.

[0019] In another aspect, the disclosure provides a method of treating relapsed or refractory multiple myeloma (RRMM) in a human subject in need thereof, said method comprising administering to said subject 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, each with from 0 to 3 amino acid modifications, 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, each with from 0 to 3 amino acid modifications.

[0020] In another aspect, the disclosure provides a method of treating relapsed or refractory multiple myeloma (RRMM) in a human subject in need thereof, said method comprising

administering to said subject 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.

[0021] In another aspect, the disclosure provides a method of treating metastatic castration resistant prostate cancer in a human subject in need thereof, said method comprising administering to said subject 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, each with from 0 to 3 amino acid modifications, 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, each with from 0 to 3 amino acid modifications.

[0022] In another aspect, the disclosure provides a method of treating metastatic castration resistant prostate cancer in a human subject in need thereof, said method comprising administering to said subject 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.

[0023] In some embodiments, the recombinant antibody for a method of treating relapsed or refractory multiple myeloma or castration resistant prostate cancer 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. In some embodiments, the effector comprises a drug. In some embodiments, the drug is an anti-cancer drug. In some embodiments, the drug is a chemotherapeutic agent. In some embodiments, the drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor. In some embodiments, the drug is a microtubule inhibitor. In some embodiments, the microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative

thereof), or maytansine (or a derivative thereof). In some embodiments, the microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF). In some embodiments, the microtubule inhibitor is monomethylauristatin E (MMAE). In some embodiments, a ratio of said effector agent to said recombinant antibody is from about 3 to about 5. In some embodiments, the ratio of said effector agent to said recombinant antibody is about 4.

[0024] In some embodiments, the effector agent for a method of treating relapsed or refractory multiple myeloma or castration resistant prostate cancer is conjugated to said recombinant antibody via a linker. In some embodiments, the linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule. In some embodiments, the linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB).

[0025] [0024][0025] In some embodiments, the recombinant antibody for a method of treating relapsed or refractory multiple myeloma or castration resistant prostate cancer 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 2.about 2.7 mg/kg, about 1.5 mg/kg, 1to 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 2.5, or7 mg/kg, about 1.8 to 2.0.about 2.5 mg/kg, about 1.8 to about 2.4 mg/kg, or about 1.8 to about 2.0 mg/kg. In some embodiments, the recombinant antibody is administered at a dose from about 1.5 to about 2.5 mg/kg. In some embodiments, the recombinant antibody 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. In some embodiments, the recombinant antibody is administered at a dose of about 1.8, about 2.4, or about 3.2 mg/kg. In some embodiments, the recombinant antibody is administered at a dose of about 1.8 mg/kg. In some embodiments, the recombinant antibody is administered at a dose of about 2.4 mg/kg. In some embodiments, the recombinant antibody is administered at a dose of about 3.2 mg/kg.

[0026] In some embodiments, the recombinant antibody for a method of treating relapsed or refractory multiple myeloma or castration resistant prostate cancer is administered to said human subject via intravenous infusion. In some embodiments, the recombinant antibody is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, every 28 days,

or every month. In some embodiments, the recombinant antibody is administered to said human subject every 21 days.

[0027] In another aspect, the disclosure provides a method of treating relapsed or refractory multiple myeloma (RRMM) in a human subject in need thereof, said method comprising administering to said subject an immunoconjugate, wherein said immunoconjugate comprises (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).

[0028] In another aspect, the disclosure provides 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. In some embodiments, immunoconjugate comprises two pairs of said adducts.

[0029] In another aspect, the disclosure provides pharmaceutical composition comprising the 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, anda 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; 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.

[0030] In another aspect, the disclosure provides 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.

[0031] In another aspect, the disclosure provides 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. In some embodiments, the pharmaceutical composition has a pH from about 5.0 to about 7.0. In some embodiments, the pharmaceutical composition comprising a pharmaceutically acceptable buffer; wherein the buffer comprises citrate, phosphate, acetate, tromethamine, histidine, succinate, malate, or α-ketoglutaric acid. In some embodiments, the pharmaceutical composition comprising a pharmaceutically acceptable buffer; wherein the buffer comprises from about 10 mM to about 30 mM histidine and the pH is from about 5 to about 7. In some embodiments, the pharmaceutical composition comprising a pharmaceutically acceptable buffer; wherein the buffer comprises

citrate, phosphate, acetate, tromethamine, histidine, succinate, malate, or α-ketoglutaric acid; wherein the buffer comprises about 20 mM histidine and the pH is about 6.0. In some embodiments, the pharmaceutical composition comprising a pharmaceutically acceptable stabilizing agent; wherein the stabilizing agent prevents denaturation of said recombinant antibody, prevents aggregation of said immunoconjugates, or both. In some embodiments, the pharmaceutical composition comprising a pharmaceutically acceptable stabilizing agent; wherein the stabilizing agent comprises a non-ionic surfactant. In some embodiments, the pharmaceutical composition comprising a pharmaceutically acceptable stabilizing agent; wherein the stabilizing agent comprises a polysorbate. In some embodiments, the pharmaceutical composition comprising a pharmaceutically acceptable stabilizing agent; wherein the stabilizing agent comprises about 0.01% polysorbate-80. In some embodiments, the pharmaceutical composition comprising an immunoconjugate, a pharmaceutically acceptable buffer, and a pharmaceutically acceptable stabilizing agent further comprising a pharmaceutically acceptable cryoprotectant. In some embodiments, the pharmaceutical composition comprising an immunoconjugate, a pharmaceutically acceptable buffer, and a pharmaceutically acceptable stabilizing agent further comprising a pharmaceutically acceptable cryoprotectant; wherein the cryoprotectant comprises a saccharide. In some embodiments, the pharmaceutical composition comprising an immunoconjugate, a pharmaceutically acceptable buffer, and a pharmaceutically acceptable stabilizing agent further comprising a pharmaceutically acceptable cryoprotectant; wherein the cryoprotectant comprises a saccharide comprising about 6% to about 10% sucrose or trehalose. In some embodiments, the pharmaceutical composition comprising an immunoconjugate, a pharmaceutically acceptable buffer, and a pharmaceutically acceptable stabilizing agent further comprising a pharmaceutically acceptable cryoprotectant; wherein the cryoprotectant is about 8.0% sucrose.

[0032] In some embodiments, the 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; 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. In some embodiments, the pharmaceutical composition comprising an effector agent; wherein said effector agent comprises a drug. In some embodiments, the pharmaceutical composition comprising an effector agent; wherein said effector agent comprises an anti-cancer drug. In some embodiments, the pharmaceutical composition comprising a drug; wherein said drug is a chemotherapeutic agent. In some embodiments, the pharmaceutical composition comprising a drug; wherein said drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor. In some embodiments, the pharmaceutical composition comprising a drug that is a microtubule inhibitor; wherein said microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative thereof), or maytansine (or a derivative thereof). In some embodiments, the pharmaceutical composition comprising a drug that is a microtubule inhibitor; wherein said microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF). In some embodiments, the pharmaceutical composition comprising an immunoconjugate comprising a recombinant antibody and an effector agent as described above; wherein a ratio of said effector agent to said recombinant antibody in a population of immunoconjugates is from about 3 to about 5. In some embodiments, the pharmaceutical composition comprising an immunoconjugate comprising a recombinant antibody and an effector agent as described above; wherein a ratio of said effector agent to said recombinant antibody in a population of immunoconjugates is about 4. In some embodiments, the pharmaceutical composition comprising an immunoconjugate comprising a recombinant antibody and an effector agent as described above; wherein said effector agent is conjugated to said recombinant antibody via a linker. In some embodiments, the pharmaceutical composition comprising an effector agent conjugated to a recombinant antibody via a linker as described above; wherein said linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule. In some embodiments, the pharmaceutical composition comprising an effector agent conjugated to a recombinant antibody via a linker as described above; wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB).

In another aspect, the disclosure provides 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. In some embodiments, the method of treating a cancer; wherein said cancer is relapsed or refractory multiple myeloma (RRMM). In some embodiments, the method of treating a cancer; wherein said cancer is metastatic castration resistant prostate cancer (mCRPC). In some embodiments, the method of treating a cancer comprising administering an immunoconjugate to the subject; wherein said immunoconjugate comprises two pairs of said adducts. In some embodiments, the method of treating a cancer as described above, further comprising detecting said CD46 in said cell. In some embodiments, the method of treating a cancer as described above, further comprising detecting said CD46 in said cell; wherein said detecting comprises immunofluorescence microscopy or immunohistochemistry. In some embodiments, the method of treating a cancer as described above, further comprising detecting said CD46 in said cell; wherein said detecting comprises flow cytometry. In some embodiments, the method of treating a cancer as described above, further comprising detecting said CD46 in said cell; wherein said detecting comprises detecting an amplification of chromosome location 1q21. In some embodiments, the method of treating a cancer as described above, wherein the immunoconjugate is administered to the human subject via intravenous infusion. In some embodiments, the method of treating a cancer as described above, wherein the immunoconjugate is administered to the human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days. In some embodiments, the method of treating a cancer as described above, wherein the immunoconjugate is administered to the human subject every 21 days over at least three cycles. In some embodiments, the method of treating a cancer as described above, wherein the immunoconjugate is administered at a dose from about 1.2 to about 3.0 mg/kg. In some embodiments, the method of treating a cancer as described above, wherein the recombinant antibody is administered at a dose of about 1.8, about 2.4, about 2.7, or about 3.0 mg/kg. In some embodiments, the method of treating a cancer as described above, wherein the weight, in kg, of the human subject in need 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. In some embodiments, the method of treating a cancer as described above, wherein the weight, in kg, of the human subject in need is an actual body weight. In some embodiments, the method of treating a cancer as described above, wherein the weight, in kg, of the human subject in need is an adjusted body weight.

[0033] In another aspect, the disclosure provides 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.

[0034] In another aspect, the disclosure provides 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. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject; 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. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject; wherein a calculated weight, in kg, of said human subject is an adjusted body weight. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject; wherein the weight, in kg, of said human subject is an actual body weight.

[0035] In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject further comprising detecting said CD46 in said cell. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject further comprising detecting said CD46 in said cell; wherein said detecting comprises immunofluorescence microscopy or immunohistochemistry. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject further comprising detecting said CD46 in said cell; wherein said detecting comprises flow cytometry. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject further comprising detecting said CD46 in said cell; wherein said detecting comprises detecting an amplification of chromosome location 1q21. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject as described above; wherein the immunoconjugate is administered to said human subject via intravenous infusion. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject as described above; wherein the immunoconjugate is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days. In some embodiments, the method of treating metastatic castration resistant prostate cancer or the method of treating relaxed or refractory multiple myeloma in a human subject as described above; wherein the immunoconjugate is administered to said human subject every 21 days over at least three cycles.

[0036] In another aspect, the disclosure provides 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 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; 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 or administered at a dose from about 1.0 to about 4.0 mg/kg. In some embodiments, the method of treating cancer; wherein said cancer is prostate cancer. In some embodiments, the method of treating prostate cancer; wherein said prostate cancer is metastatic castration resistant prostate cancer. In some embodiments, the method of treating cancer; wherein said cancer is multiple myeloma. In some embodiments, the method of treating multiple myeloma; wherein multiple myeloma is relapsed or refractory multiple myeloma. In some embodiments, the method of treating cancer as described above further comprising detecting CD46 expression in a cell of said cancer. In some embodiments, the method of treating cancer as described above further comprising detecting CD46 expression in a cell of said cancer, wherein said detecting comprises immunofluorescence microscopy or immunohistochemistry. In some embodiments, the method of treating cancer as described above further comprising detecting CD46 expression in a cell of said cancer, wherein said detecting comprises flow cytometry. In some embodiments, the method of treating cancer as described above further comprising detecting CD46 expression in a cell of said cancer, wherein said detecting comprises detecting an amplification of chromosome location 1q21. In some embodiments, the method of treating cancer as described above; 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. In some embodiments, the method of treating cancer as described above; wherein said cancer comprises a copy number increase of chromosome band 1q21. In some embodiments, the method of treating cancer as described above; wherein the 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. In some embodiments, the method of treating cancer as described above; wherein the immunoconjugate is administered at a dose of from about 1.2 to about 3.0 mg/kg. In some embodiments, the method of treating cancer as described above; wherein the 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. In some embodiments, the method of treating cancer as described above; wherein the immunoconjugate is administered at a dose of about 1.8, about 2.4, about 2.7, or about 3.0 mg/kg. In some embodiments, the method of treating cancer as described above; wherein the immunoconjugate is administered at a dose of about 1.8 mg/kg. In some embodiments, the method of treating cancer as described above; wherein the immunoconjugate is administered at a dose of about 2.4 mg/kg. In some embodiments, the method of treating cancer as described above; wherein the immunoconjugate is administered at a dose of about 2.7 mg/kg. In some embodiments, the method of treating cancer as described above; wherein the immunoconjugate is administered at a dose of about 3.0 mg/kg. In some embodiments, the method of treating cancer in a human subject as described above; 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. In some embodiments, the method of treating cancer in a human subject as described above; wherein the weight, in kg, of said human subject is an actual body weight. In some embodiments, the method of treating cancer in a human subject as described above; wherein the weight, in kg, of said human subject is an adjusted body weight. In some embodiments, the method of treating cancer in a human subject, said method comprising administering to said human subject an immunoconjugate comprising recombinant antibody as described above; wherein the recombinant antibody is administered to said human subject via intravenous infusion. In some embodiments, the method of treating cancer in a human subject, said method comprising administering to said human subject an immunoconjugate comprising recombinant antibody as described above; wherein the recombinant antibody is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days. In some embodiments, the method of treating cancer in a human subject, said method comprising administering to said human subject an immunoconjugate comprising recombinant antibody as described above; wherein the recombinant antibody is administered to said human subject every 21 days over at least three cycles. In some embodiments, the method of treating cancer in a human subject, said method comprising administering to said human subject an immunoconjugate comprising the effector agent as described above; 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. In some embodiments, the method of treating cancer in a human subject, said method comprising administering to said human subject an immunoconjugate comprising the effector agent as described above; wherein said effector agent comprises a drug. In some embodiments, the method of treating cancer in a human subject as described above; wherein the effector agent comprises an anti-cancer drug. In some embodiments, the method of treating cancer in a human subject as described above; wherein the effector agent comprises a drug; wherein said drug is a chemotherapeutic agent. In some embodiments, the method of treating cancer in a human subject as described above; wherein the effector agent comprises a drug; wherein said drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor. In some embodiments, the method of treating cancer in a human subject as described above; wherein the effector agent comprises a drug; wherein said drug is a microtubule inhibitor. In some embodiments, the method of treating cancer in a human subject as described above; wherein the microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative thereof), or maytansine (or a derivative thereof). In some embodiments, the method of treating cancer in a human subject as described above; wherein the microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF). In some embodiments, the method of treating cancer in a human subject as described above; wherein the microtubule inhibitor is monomethylauristatin E (MMAE). In some embodiments, the method of treating cancer in a human subject, said method comprising administering to said human subject an immunoconjugate comprising the effector agent and the recombinant antibody as described above; wherein a ratio of said effector agent to said recombinant antibody is from about 3 to about 5. In some embodiments, the method of treating cancer in a human subject as described above; wherein a ratio of said effector agent to said recombinant antibody is about 4. In some embodiments, the method of treating cancer in a human subject as described above; wherein said effector agent is conjugated to said recombinant antibody via a linker. In some embodiments, the method of treating cancer in a human subject as described above; wherein said linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule. In some embodiments, the method of treating cancer in a human subject as described above; wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB). In some embodiments, the method of treating cancer in a human subject as described above; wherein said immunoconjugate binds CD46 expressed on the surface of a cell and is internalized into said cell. In some embodiments, the method of treating cancer in a human subject as described above; wherein said immunoconjugate is internalized into said cell via macropinocytosis.

[0037] In another aspect, the disclosure provides 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; for use in the treatment of a cancer in a human subject comprising a cell expressing CD46. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above, wherein said cancer is relapsed or refractory multiple myeloma (RRMM). In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above, wherein said cancer is metastatic castration resistant prostate cancer (mCRPC). In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above, wherein said immunoconjugate comprises two pairs of said adducts. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject comprising a cell expressing CD46 as described above, wherein said cell comprises CD46 as determined by immunofluorescence microscopy or immunohistochemistry. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject comprising a cell expressing CD46 as described above, wherein said cell comprises CD46 as determined by flow cytometry. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject comprising a cell expressing CD46 as described above, wherein said cell comprises an amplification of chromosome location 1q21. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above, wherein said immunoconjugate is formulated for intravenous infusion. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above, 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. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above, wherein said immunoconjugate is administered to said human subject every 21 days. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above, wherein said immunoconjugate is administered

at a dose from about 1.2 to about 3.0 mg/kg. In some embodiments, the immunoconjugate comprising a recombinant antibody for use in the treatment of a cancer in a human subject as described above, 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. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above; 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. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above; wherein the weight, in kg, of said human subject is an actual body weight. In some embodiments, the immunoconjugate for use in the treatment of a cancer in a human subject as described above; wherein the weight, in kg, of said human subject is an adjusted body weight.

[0038] In another aspect, the disclosure provides 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.

[0039] In another aspect, the disclosure provides 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.

[0040] In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma in a human subject wherein the 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. In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma in a human subject wherein the weight, in kg, of said human subject is an actual body weight. In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma in a human subject wherein the weight, in kg, of said human subject is an adjusted body weight. In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma in a human subject comprising a cell; wherein said cell comprises CD46 as determined by immunofluorescence microscopy or immunohistochemistry. In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma in a human subject comprising a cell; wherein said cell comprises CD46 as determined by flow cytometry. In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma in a human subject comprising a cell; wherein said cell comprises an amplification of chromosome location 1q21. In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma in a human subject; wherein said immunoconjugate is formulated for intravenous infusion. In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma in a human subject; 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. In some embodiments, the immunoconjugate for the treatment of metastatic castration resistant prostate cancer or for the treatment of refractory multiple myeloma

in a human subject; wherein said immunoconjugate is administered to said human subject every 21 days over at least three cycles.

[0041] In another aspect, the disclosure provides 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. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said cancer is prostate cancer. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said prostate cancer is metastatic castration resistant prostate cancer. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said prostate cancer is multiple myeloma. In some embodiments, the immunoconjugate for treating multiple myeloma in a human subject; wherein said multiple myeloma is relapsed or refractory multiple myeloma. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said cancer comprises a cell that expresses CD46 as determined by immunofluorescence microscopy or immunohistochemistry. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said cancer comprises a cell that expresses CD46 as determined by flow cytometry. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said cancer comprises an amplification of chromosome location 1q21. In some embodiments, the immunoconjugate for treating cancer in a human subject; 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. In some embodiments, the immunoconjugate for treating cancer in a human subject; 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. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said immunoconjugate is administered at a dose from about 1.2 to about 3.0 mg/kg. In some embodiments, the immunoconjugate for treating cancer in a human subject; 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. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said immunoconjugate is administered at a dose of about 1.8, about 2.4, about 2.7, or about 3.0 mg/kg. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said immunoconjugate is administered at a dose of about 1.8, about 2.4, about 2.7, or about 3.0 mg/kg. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said immunoconjugate is administered at a dose of about 1.8 mg/kg. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said immunoconjugate is administered at a dose of about 2.4 mg/kg. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said immunoconjugate is administered at a dose of about 2.7 mg/kg. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein said immunoconjugate is administered at a dose of about 3.0 mg/kg. In some embodiments, the immunoconjugate for treating cancer in a human subject; 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. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein the weight, in kg, of said human subject is an actual body weight. In some embodiments, the immunoconjugate for treating cancer in a human subject; wherein the weight, in kg, of said human subject is an adjusted body weight. In some embodiments, the immunoconjugate comprising the recombinant antibody for treating cancer in a human subject; wherein said recombinant antibody is formulated for intravenous infusion. In some embodiments, the immunoconjugate comprising the recombinant antibody for treating cancer in a human subject; 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. In some embodiments, the immunoconjugate comprising the recombinant antibody for treating cancer in a human subject; wherein said recombinant antibody is administered to said human subject every 21 days. In some embodiments,

the immunoconjugate comprising the effector agent for treating cancer in a human subject; 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. In some embodiments, the immunoconjugate comprising the effector agent for treating cancer in a human subject; wherein said effector agent comprises a drug. In some embodiments, the immunoconjugate comprising the effector agent for treating cancer in a human subject; wherein said effector agent comprises an anti-cancer drug. In some embodiments, the immunoconjugate comprising the effector agent; wherein said effector agent comprises a chemotherapeutic agent. In some embodiments, the immunoconjugate comprising the effector agent; wherein said effector agent comprises a drug; wherein said drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor. In some embodiments, the immunoconjugate comprising a microtubule inhibitor, wherein said microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative thereof), or maytansine (or a derivative thereof). In some embodiments, the immunoconjugate comprising a microtubule inhibitor, wherein said microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF). In some embodiments, the immunoconjugate comprising the effector agent; wherein said effector agent comprises a drug; wherein said drug is a microtubule inhibitor, wherein said microtubule inhibitor is monomethylauristatin E (MMAE). In some embodiments, the immunoconjugate comprising the effector agent and the recombinant antibody; wherein a ratio of said effector agent to said recombinant antibody is from about 3 to about 5. In some embodiments, the immunoconjugate comprising the effector agent and the recombinant antibody; wherein a ratio of said effector agent to said recombinant antibody is from about 4. In some embodiments, the immunoconjugate comprising the effector agent and the recombinant antibody; wherein said effector agent is conjugated to said recombinant antibody via a linker. In some embodiments, the immunoconjugate comprising the effector agent conjugated to the recombinant antibody via a linker; wherein said linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule. In some embodiments, the immunoconjugate comprising the effector agent conjugated to the recombinant antibody via a linker; wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB). In some embodiments, the immunoconjugate comprising the effector agent and the recombinant antibody; wherein said immunoconjugate binds CD46 expressed on the surface of a cell and is internalized into said cell. In some embodiments, the immunoconjugate comprising the effector agent and the recombinant antibody; wherein said immunoconjugate is internalized into said cell via macropinocytosis.

[0042] In another aspect, the disclosure provides a pharmaceutical formulation for the treatment of metastatic castration resistant prostate cancer in a human subject in need thereof comprising an immunoconjugate 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 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.

[0043] In another aspect, the disclosure provides 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, about 20 mM histidine buffer, about 8.0% sucrose, about 0.01% polysorbate 80; and wherein said 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.

BRIEF DESCRIPTION OF THE FIGURES

[0044] FIG. 1 depicts flow cytometry traces showing YS5FL binding to prostate cells.

[0045] FIG. 2 depicts flow cytometry traces showing YS5FL binding to multiple myeloma cells.

[0046] FIG. 3 is a diagram showing the structure of the FOR46 immunoconjugate described herein.

[0047] FIG. 4 is a hydrophobic interaction chromatography trace showing the stoichiometry of MMAE conjugation to YS5FL in FOR46.

[0048] FIG. 5A is a CT scan showing metastatic lesions in castration resistant prostate cancer patient 001-09-28 (dosed at 2.7 mg/kg FOR46) at Cycle 3 Day 15 and before treatment.

[0049] FIG. 5B is a graph illustrating a reduction in serum PSA in patient 001-09-28.

[0050] FIG. 6 is a swimmer plot showing the status of patients in the prostate cancer dose escalation trial. PR: partial response; EOS: end of study; EOT: end of treatment; PD: progressive disease.

[0051] FIG. 7A is graph showing the response of multiple myeloma patient 006-05-008 to treatment with 1.8 mg/kg FOR46.

[0052] FIG. 7B is graph showing the response of multiple myeloma patient 001-06-012 to treatment with 2.4 mg/kg FOR46.

[0053] FIG. 7C is graph showing the response of multiple myeloma patient 003-06-014 to treatment with 2.4 mg/kg FOR46.

[0054] FIG. 8 is a swimmer plot showing the status of patients in the multiple myeloma dose escalation and extension trials. EOS: end of study; EOT: end of treatment; PD: progressive disease.

DETAILED DESCRIPTION

[0055] CD46, also known as CD46 complement regulatory protein, cluster of differentiation 46 and membrane cofactor protein, is an inhibitory complement receptor. Overexpression of CD46 has been observed in several cancers, such as breast cancer, colorectal cancer, liver cancer, lung cancer, or prostate cancer. In some cases, overexpression of CD46 has been characterized as a negative prognostic factor. For example, overexpression of CD46 has been correlated with shorter progression-free time and shorter overall survival time in breast cancer patients and ovarian cancer patients. Provided herein are antibodies and immunoconjugates targeting CD46 for the treatment of cancer. Further provided herein are specific dosing and administration regimes for administering the CD46 targeting antibodies and immunoconjugates to human subjects in need thereof. Further provided herein are formulations of CD46 targeting antibodies and immunoconjugates for administration to a subject in need thereof, that provide e.g., sufficient stability, cryoprotection etc.

Definitions

[0056] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. In this application, the use of the singular includes the plural unless specifically stated otherwise. It is noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[0057] As used herein, ranges and amounts can be expressed as "about" a particular value or range. About also includes the exact amount. Hence "about 5 μL" means "about 5 μL" and also "5 μL." Generally, the term "about" includes an amount that would be expected to be within experimental error.

[0058] The terms "antibody" and "immunoglobulin" are used interchangeably herein and are used in the broadest sense and covers fully assembled antibodies, antibody fragments that can bind antigen, for example, Fab, F(ab')2, Fv, single chain antibodies (scFv), diabodies, antibody chimeras, hybrid antibodies, bispecific antibodies, and the like.

[0059] The terms "monoclonal antibody" and "mAb" are used interchangeably herein and refer to an antibody obtained from a substantially homogeneous population of antibodies, i.e., the individual antibodies of the population are identical except for possible naturally occurring mutations that may be present in minor amounts.

[0060] The terms "native antibodies" and "native immunoglobulins" are heterotetrameric glycoproteins of about 150,000 Daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light and heavy-chain variable domains.

[0061] The term "hypervariable region," as used herein, refers to the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarily determining region" or "CDR" (i.e., residues 24-34 (L1), 50-56 (L2), and 89-97 (L3) in the light-chain variable domain and 31-35 (H1), 50-65 (H2), and 95-102 (H3) in the heavy-chain variable domain; Kabat et al. (1991) Sequences of Proteins of Immunological Interest Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242 (referred to herein as "Kabat et al") and/or those residues from a "hypervariable loop" (i.e., residues 26-32 (L1), 50-52 (L2), and 91-96 (L3) in the light-chain variable domain and (H1), 53-55 (H2), and 96-101 (13) in the heavy chain variable domain; Chothia and Lesk, (1987) J. Mol. Biol., 196:901-917). "Framework" or "FR" residues are those variable domain residues other than the hypervariable region residues, as herein deemed.

[0062] In some instances, the CDRs of an antibody is determined according to (i) the Kabat numbering system Kabat et al. (1991) Sequences of Proteins of Immunological Interest Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; or (ii) the Chothia numbering scheme, which will be referred to herein as the "Chothia CDRs" (see, e.g., Chothia and Lesk, 1987, J. Mol. Biol., 196:901-917; Al-Lazikani et al., 1997, J. Mol. Biol., 273 :927-948; Chothia et al., 1992, J. Mol. Biol., 227:799-817; Tramontano A et al. , 1990, J. Mol. Biol. 215(1): 175-82; and U.S. Patent No. 7,709,226); or (iii) the ImMunoGeneTics (IMGT) numbering system, for example, as described in Lefranc, M.-P., 1999, The Immunologist, 7: 132-136 and Lefranc, M.-P. et al, 1999, Nucleic Acids Res., 27:209-212 ("IMGT CDRs"); or (iv) MacCallum et al, 1996, J. Mol. Biol., 262:732-745. See also, e.g., Martin, A., "Protein Sequence and Structure Analysis of Antibody Variable Domains," in Antibody Engineering, Kontermann and Diibel, eds., Chapter 31, pp. 422-439, Springer- Verlag, Berlin (2001).

[0063] With respect to the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35 A and 35B) (CDRl), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDRl), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). As is well known to those of skill in the art, using the Kabat numbering system, the actual linear amino acid sequence of the antibody variable domain can contain fewer or additional amino acids due to a shortening or lengthening of a FR and/or CDR and, as such, an amino acid's Kabat number is not necessarily the same as its linear amino acid number.

[0064] As used herein, the term "antigen-binding site" refers to the part of the antigen binding molecule that specifically binds to an antigenic determinant. More particularly, the term "antigen-binding site" refers the part of an antibody that comprises the area which specifically binds to and is complementary to part or all of an antigen. Where an antigen is large, an antigen binding molecule may only bind to a particular part of the antigen, which part is termed an epitope. An antigen-binding site may be provided by, for example, one or more variable domains (also called variable regions). Preferably, an antigen-binding site comprises an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH).

[0065] By "specific binding" is meant that the binding is selective for the antigen and can be discriminated from unwanted or non-specific interactions. The ability of an antigen binding molecule to bind to a specific antigen can be measured either through an enzyme-linked immunosorbent assay (ELISA) or other techniques familiar to one of skill in the art, e.g. Surface Plasmon Resonance (SPR) technique (analyzed on a BIAcore instrument) (Liljeblad et al., Glyco J 17, 323-329 (2000)), and traditional binding assays (Heeley, Endocr Res 28, 217-229 (2002)). In one embodiment, the extent of binding of an antigen binding molecule to an unrelated protein is less than about 10% of the binding of the antigen binding molecule to the antigen as measured, e.g. by SPR. In certain embodiments, an molecule that binds to the antigen has a dissociation constant (Kd) of ≤1 μM, ≤100 nM, ≤10 nM, ≤1 nM, ≤0.1 nM, ≤0.01 nM, or ≤0.001 nM (e.g. 10−7 M or less, e.g. from 10−7M to 10−13 M, e.g. from 10−9 M to 10−13 M).

[0066] Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of human immunoglobulins: IgA, IgD, IgE, IgG, IgM, and IgY , and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known. Different isotypes have different effector functions. For example, human IgG1 and IgG3 isotypes have ADCC (antibody dependent cell-mediated cytotoxicity) activity. The light chains of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[0067] The term "chimeric antibody," as used herein refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source (e.g., protein) or species, while the remainder of the heavy and/or light chain is derived from a different source (e.g., protein) or species.

[0068] The term "recombinant human antibody," as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from a host cell such as a NSO or CHO cell or from an animal (e.g. a mouse) that is transgenic for human immunoglobulin genes or antibodies expressed using a recombinant expression vector transfected into a host cell. Such recombinant human antibodies have variable and constant regions in a rearranged form. In some cases, the recombinant human antibodies have been subjected to in vivo somatic hypermutation. Thus, the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germ line VH and VL sequences, may not naturally exist within the human antibody germ line repertoire in vivo.

[0069] The term "valent" as used herein denotes the presence of a specified number of binding sites in an antigen binding molecule. As such, the terms "bivalent", "tetravalent", and "hexavalent" denote the presence of two binding sites, four binding sites, and six binding sites, respectively, in an antigen binding molecule. The bispecific antibodies according to the invention are at least "bivalent" and may be "trivalent" or "multivalent" (e.g. "tetravalent" or "hexavalent"). In a particular aspect, the antibodies of the present invention have two or more binding sites and are bispecific. That is, the antibodies may be bispecific even in cases where there are more than two binding sites (i.e. that the antibody is trivalent or multivalent). In particular, the invention relates to bispecific bivalent antibodies, having one binding site for each antigen they specifically bind to.

[0070] The term "monospecific" antibody as used herein denotes an antibody that has one or more binding sites each of which bind to the same epitope of the same antigen.

[0071] The terms "individual(s)", "subject(s)" and "patient(s)" are used interchangeably herein and refer to any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g. constant or intermittent) of a health care worker (e.g. a doctor, a registered nurse, a nurse practitioner, a physician's assistant, an orderly or a hospice worker).

[0072] As used herein, the term "percent (%) amino acid sequence identity" with respect to a sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as EMBOSS MATCHER, EMBOSS WATER, EMBOSS STRETCHER, EMBOSS NEEDLE,

EMBOSS LALIGN, BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0073] The terms "cancer" and "tumor" are used interchangeably herein, encompass all types of oncogenic processes and/or cancerous growths. In embodiments, cancer includes primary tumors as well as metastatic tissues or malignantly transformed cells, tissues, or organs. In embodiments, cancer encompasses all histopathologies and stages, e.g., stages of invasiveness/severity, of a cancer. In embodiments, cancer includes relapsed and/or resistant cancer.

[0074] As used herein, "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, the molecules of the invention are used to delay development of a disease or to slow the progression of a disease.

[0075] As used herein, "ideal body weight" ("IBW") is 50 kg + 2.3 kg x (Actual height – 60 in) for males and 45.5 kg + 2.3 kg x (Actual height – 60 in) for females.

[0076] As used herein, "adjusted body weight" ("AJBW") is IBW + 0.4 x (Actual weight – IBW).

Anti-CD46 Recombinant Antibodies

[0077] In some embodiments, disclosed herein is a recombinant antibody (or antigen binding fragment thereof) that specifically binds CD46. In some embodiments, antibody or antigen binding fragment or variant thereof is a monoclonal antibody. In some embodiments, antibody or antigen binding fragment or variant thereof is a human antibody, a murine antibody, a humanized antibody, or a chimeric antibody. In some embodiments, the antibody comprises or consists of a function fragment of a full length antibody (e.g., an antigen binding fragment of a full length antibody) such as a monovalent Fab, a bivalent Fab'2, a single-chain variable fragment (scFv), or functional fragment or variant thereof. In some embodiments, the recombinant antibody (or antigen binding fragment thereof) comprises an immunoglobulin variable heavy chain domain (VH). In some embodiments, the recombinant antibody (or antigen binding fragment thereof) comprises an immunoglobulin variable light chain domain (VL). In some embodiments, the recombinant antibody (or antigen binding fragment thereof) comprises a VH and a VL.

[0078] In some embodiments, the recombinant antibody (or antigen binding fragment thereof) comprises an Fc region. In some embodiments, the recombinant antibody (or antigen binding fragment thereof) is a full length antibody. In some embodiments, the recombinant antibody (or antigen binding fragment thereof) comprises a first light chain that comprises a light chain variable region and a light chain constant region; a first heavy chain that comprises a heavy chain variable region and a heavy chain constant region; a second light chain that comprises a light chain variable region and a light chain constant region; and a second heavy chain that comprises a heavy chain variable region and a heavy chain constant region. In some embodiments, the first and second light chains have at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity. In some embodiments, the first and second light chains bind the same epitope. In some embodiments, the first and second heavy chains have at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity. In some embodiments, the first and second heavy chains bind the same epitope.

[0079] In some embodiments, the recombinant antibody (or antigen binding fragment thereof) is derived from non-human (e.g. rabbit or mouse) antibodies. In some instances, the humanized form of the non-human antibody contains a minimal non-human sequence to maintain original antigenic specificity. In some cases, the humanized antibodies are human immunoglobulins (acceptor antibody), wherein the CDRs of the acceptor antibody are replaced by residues of the CDRs of a non-human immunoglobulin (donor antibody), such as rat, rabbit, or mouse donor having the desired specificity, affinity, avidity, binding kinetics, and/or capacity. In some instances, one or more framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues of the donor antibody.

Complementarity Determining Regions (CDRs)

[0080] In some embodiments, the CD46 binding recombinant antibody comprises an immunoglobulin variable heavy chain domain (VH) that comprises at least one, two, or three complementarity determining regions (CDRs) disclosed in Table 1 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0081] In some embodiments, the CD46 binding recombinant antibody comprises an immunoglobulin variable light chain domain (VL) that comprises at least one, two, or three complementarity determining regions (CDRs) disclosed in Table 2 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0082] In some embodiments, the CD46 binding recombinant antibody comprises a VH that comprises at least one, two, or three complementarity determining regions (CDRs) disclosed in

Table 1 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity); and a VL that comprises at least one, two, or three complementarity determining regions (CDRs) disclosed in Table 2 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0083] In some embodiments, the CD46 binding recombinant antibody comprises a VH that comprises a CDR1 of SEQ ID NO: 1, a CDR2 of SEQ ID NO: 2, and a CDR3 of SEQ ID NO: 3.

[0084] In some embodiments, the CD46 binding recombinant antibody comprises a VL that comprises a CDR1 of SEQ ID NO: 4, a CDR2 of SEQ ID NO: 5, and a CDR3 of SEQ ID NO: 6.

[0085] In some embodiments, the CD46 binding recombinant antibody comprises a VH that comprises a CDR1 of SEQ ID NO: 1, a CDR2 of SEQ ID NO: 2, and a CDR3 of SEQ ID NO: 3; and a VL that comprises a CDR1 of SEQ ID NO: 4, a CDR2 of SEQ ID NO: 5, and a CDR3 of SEQ ID NO: 6.

Table 1. VH CDR amino acid sequences of anti-CD46 antibodies as defined by Kabat et al.

Antibody	SEQ ID NO	CDR1	SEQ ID NO	CDR2	SEQ ID NO	CDR3
YS5FL	1	GLTVNNYA	2	ISYDGNNK	3	AKGGGYFDL

Table 2. VL CDR amino acid sequences of anti-CD46 antibodies as defined by Kabat et al.

Antibody	SEQ ID NO	CDR1	SEQ ID NO	CDR2	SEQ ID NO	CDR3
YS5FL	4	SSNIGAGYD	5	GNN	6	SSYTSGTWL

[0086] In some embodiments, a CDR described herein comprises one, two, or three amino acid modifications. In some embodiments, said modification is a substitution, addition, or deletion. In some embodiments, a CDR described herein comprises one, two, or three conservative amino acid substitutions. In some embodiments, the one, two, or three amino acid modifications does not substantially modify binding to human CD46. In some embodiments, the one, two, or three amino acid modifications modifies binding to human CD46. In some embodiments, a VH-CDR3 and/or VL-CDR3 comprises an amino acid substitution that modifies binding to human CD46, immunogenicity, or some other feature. In some embodiments, the amino acid substitution is an alanine (A).

Variable Heavy and Variable Light Regions

[0087] In some embodiments, the CD46 binding recombinant antibody comprises a VH that comprises an amino acid sequence disclosed in Table 3 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0088] In some embodiments, the CD46 binding recombinant antibody comprises a VL that comprises an amino acid sequence disclosed in Table 4 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0089] In some embodiments, the CD46 binding recombinant antibody comprises a VH that comprises an amino acid sequence disclosed in Table 3 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity); and a VL that comprises an amino acid sequence disclosed in Table 4 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0090] In some embodiments, the CD46 binding recombinant antibody comprises a VH that comprises an amino acid sequence of SEQ ID NO: 7, or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0091] In some embodiments, the CD46 binding recombinant antibody comprises a VL that comprises an amino acid sequence of SEQ ID NO: 8, or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0092] In some embodiments, the CD46 binding recombinant antibody comprises a VH that comprises an amino acid sequence of SEQ ID NO: 7, or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity); and a VL that comprises an amino acid sequence of SEQ ID NO: 8, or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

Table 3. Amino acid sequence of the anti-CD46 variable heavy chain binding domains.

Name	SEQ ID NO	Amino Acid Sequence
YS5FL	7	QVQLVQSGGGVVQPGRSLRLACAASGLTVNNYAMHWVRQAPGK GLEWVAVISYDGNNKYYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCAKGGGYFDLWGRGTLVTVSS

Table 4. Amino acid sequence of the anti-CD46 variable light chain binding domains.

Name	SEQ ID NO	Amino Acid Sequence
YS5FL	8	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGT APKLLIYGNNNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADY YCSSYTSGTWLFGGGTKLTVL

Heavy Chain and Light Chains

[0093] In some embodiments, the CD46 binding recombinant antibody comprises a heavy chain that comprises an amino acid sequence disclosed in Table 5 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0094] In some embodiments, the CD46 binding recombinant antibody comprises a light chain that comprises an amino acid sequence disclosed in Table 6 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0095] In some embodiments, the CD46 binding recombinant antibody comprises a heavy chain that comprises an amino acid sequence disclosed in Table 5 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity); and a light chain that comprises an amino acid sequence disclosed in Table 6 or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0096] In some embodiments, CD46 binding recombinant antibody comprises a heavy chain that comprises an amino acid sequence of SEQ ID NO: 9, or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0097] In some embodiments, the CD46 binding recombinant antibody comprises a light chain that comprises an amino acid sequence of SEQ ID NO: 10, or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

[0098] In some embodiments, the CD46 binding recombinant antibody comprises a heavy chain that comprises an amino acid sequence of SEQ ID NO: 9, or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity); and a light chain that comprises an amino acid sequence of SEQ ID NO: 10, or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

Table 5. Amino acid sequence of the anti-CD46 heavy chain.

Name	SEQ ID NO	Amino Acid Sequence
YS5FL	9	QVQLVQSGGGVVQPGRSLRLACAASGLTVNNYAMHWVRQAPGK GLEWVAVISYDGNNKYYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCAKGGGYFDLWGRGTLVTVSSASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK

Table 6. Amino acid sequence of the anti-CD46 light chain.

Name	SEQ ID NO	Amino Acid Sequence
YS5FL	10	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGT APKLLIYGNNNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADY YCSSYTSGTWLFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

[0099] In some embodiments, the aanti-CD46 antibody disclosed herein comprises an immunoglobulin constant region (e.g., an Fc region). Exemplary Fc regions can be chosen from the heavy chain constant regions of IgG1, IgG2, IgG3, or IgG4; more particularly, the heavy chain constant region of human IgG1 or IgG4. In some embodiments, the immunoglobulin constant region (e.g., the Fc region) is altered, e.g., mutated, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function.

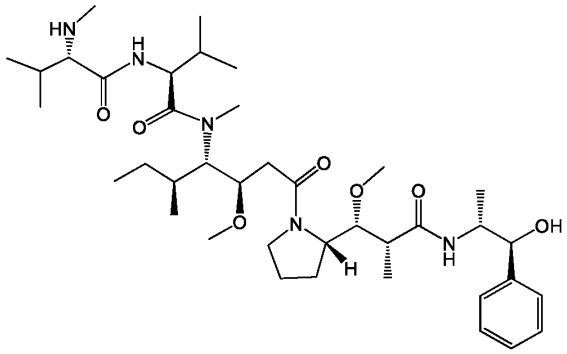
Effector Agents

[00100] In some embodiments, disclosed herein are immunoconjugates that comprise an anti-CD46 antibodies attached to an effector agent (or prodrug thereof). In some embodiments, the effector agent is a drug (or prodrug thereof), small molecule, protein, peptide, antibody, ligand, receptor, cytotoxic agent, cytostatic agent, liposome, nanoparticle, radionuclide, cytokine, chemokine, a toxin, a detectable label, a viral particle, or a chelate.

[00101] In some embodiments, the effector agent is a drug (or prodrug thereof). In some embodiments, the effector agent is an anti-cancer agent (or prodrug thereof). In some embodiments, the effector agent is a chemotherapeutic agent (or prodrug thereof). In some embodiments, the effector agent is a microtubule inhibitor (or prodrug thereof), a DNA-damaging agent (or prodrug thereof), or a polymerase inhibitor (or prodrug thereof).

[00102] In some embodiments, the effector agent is a microtubule inhibitor (or prodrug thereof). In some embodiments, the microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative thereof), or maytansine (or a derivative thereof). In some embodiments, the microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF). In some embodiments, the microtubule inhibitor is monomethylauristatin E (MMAE).

[00103] In some embodiments, the effector agent comprises or consists of a compound of Formula A:



(Formula A)

Molecular formula: $C_{39}H_{67}N_5O_7$

[00104] In certain embodiments, the effector comprises a detectable label. Suitable detectable labels include, but are not limited to radio-opaque labels, nanoparticles, PET labels, MRI labels, radioactive labels, and the like. Among the radionuclides and useful in various embodiments of the present invention, gamma-emitters, positron-emitters, x-ray emitters, and fluorescence-emitters are suitable for localization, diagnosis and/or staging, and/or therapy, while beta and alpha-emitters and electron and neutron-capturing agents, such as boron and uranium, also can be used for therapy.

Immunoconjugates

[00105] In one aspect, provided herein are immunoconjugates comprising an anti-CD46 antibody and an effector agent. In some embodiments, the methods described herein utilize these immunoconjugates.

[00106] In some embodiments, the immunoconjugate comprises an anti-CD46 antibody (or antigen binding fragment thereof) described herein. In some embodiments, the immunoconjugate comprises a YS5FL antibody (or antigen binding fragment thereof).

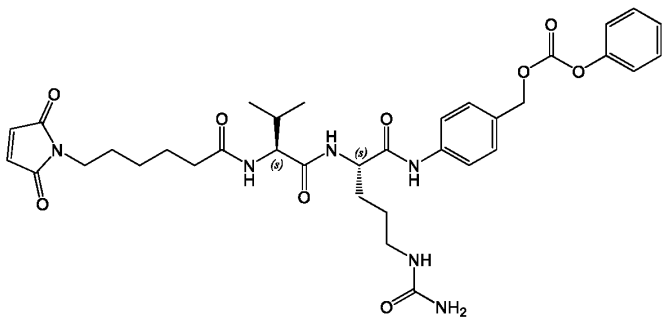
[00107] In some embodiments, the effector agent is conjugated to the anti-CD46 antibody. In some embodiments, the effector agent is attached to the anti-CD46 antibody via a liker. In some embodiments, the linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule. Exemplary peptide linkers include, but are not limited to, peptide linkers comprising glycine, serine, or glycine and serine.

[00108] In some embodiments, the linker is cleavable. In some embodiments, the linker is cleaved only upon internalization into a cell. In some embodiments, the cleavable linker is only cleavable

upon internalization into a cancer cell. In some embodiments, the cleavable portion of a linker is a peptide (e.g., a dipeptide, e.g., ValCit). In some embodiments, the cleavable linker is cleavable by cathepsin. In some embodiments, the linker comprises maleimide. In some embodiments, the linker comprises caproic acid. In some embodiments, the linker comprises maleimide and caproic acid. In some embodiments, the linker comprises maleimide, caproic acid, and a cleavable dipeptide.

[00109] In some embodiments, the linker comprises or consists of is a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB).

[00110] In some embodiments, the linker comprises or consists of a compound of Formula B:



(Formula B)

[00111] In some embodiments, an effector agent is attached to a light chain of the anti-CD46 antibody. In some embodiments, an effector agent is attached to a light chain constant region of the anti-CD46 antibody. In some embodiments, an effector agent is attached to a heavy chain of the anti-CD46 antibody. In some embodiments, an effector agent is attached to a heavy chain constant region of the anti-CD46 antibody.

[00112] In some embodiments, an effector moiety is attached to a cysteine residue of the anti-CD46 antibody. In some embodiments, an anti-CD46 antibody is partially reduced prior to conjugation to an effector moiety such that 1-4 interchain disulfide bonds are reduced while intrachain disulfide bonds are not reduced. Partial reduction exposes pairs of cysteine residues, rendering them accessible to conjugation to adducts such as mc-vc-PAB-MMAE. In some embodiments, the following interchain cysteine pairs of YS5FL are exposed: 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 some embodiments, an effector such as mc-vc-PAB-MMAE is conjugated to 0, 1, 2, 3, or 4 pairs of cysteine residues on YS5FL.

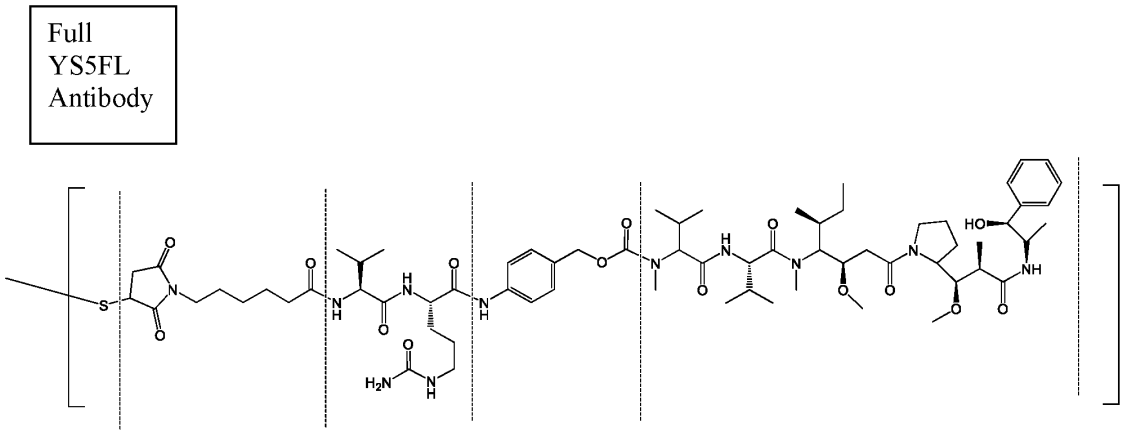
[00113] In some embodiments, the ratio of effector agents to anti-CD46 antibodies is c. In some embodiments, the ratio of effector agents to anti-CD46 antibodies is 2:1, 4:1, 6:1, or 8:1. In some

embodiments, the ratio of effector agents to anti-CD46 antibodies is about 4:1. In some embodiments, the average ratio of effector agents to anti-CD46 antibodies is about 3.7:1. In some embodiments, if the immunoconjugate comprises 2 or more effector agents, each effector agent is the same. In some embodiments, if the immunoconjugate comprises 2 or more effector agents, at least two effector agents are different. In some embodiments, the ratio of effector agents to anti-CD46 antibodies is about 4:1 and each effector agent is the same.

Exemplary Immunoconjugate

[00114] An exemplary immunoconjugate provided herein comprises an anti-CD46 YS5FL antibody linked to a monomethyl auristatin E (MMAE) effector agent via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB). In some embodiments, the ratio of MMAE to YSFL antibody is about 4:1.

[00115] In some embodiments, the immunoconjugate comprises the antibody conjugate below in Formula C, wherein the comprises heavy chain of SEQ ID NO: 9; and a light chain of SEQ ID NO: 10. This immunoconjugate is also referred to herein as FOR46 and comprises YS5FL antibody attached to MMAE through a mc-vc-PAB linker.



Formula C

[00116] In some embodiments, an anti-CD46 immunoconjugate described herein is manufactured by a process comprising reduction or partial reduction of disulfide bonds of an immunoglobulin. In some embodiments, an anti-CD46 immunoconjugate described herein is manufactured by a process comprising reduction or partial reduction of interchain disulfide bonds of an immunoglobulin. In some embodiments, the reducing agent is dithiothreitol (DTT) or tris(2-

carboxyethyl)phosphine (TCEP). In some embodiments, an effector-linker complex comprising a maleimide reactive group is conjugated to pairs of reduced cysteines of an immunoglobulin. In some embodiments, the effector-linker complex is mc-vc-PAB-MMAE.

[00117] In some embodiments, an effector-linker complex is conjugated at C219, C225, or C228 of a YS5FL heavy (SEQ ID NO: 9) or C214 of a YS5FL light chain (SEQ ID NO: 10), or any combination thereof. In some embodiments, the effector-linker complexes are conjugated to C219 of a YS5FL heavy chain and C214 of a YS5FL light chain. In some embodiments, an anti-CD46 immunoconjugate comprises two YS5FL heavy chains and two YS5FL light chains and effector-linker complexes are conjugated to C219 of a YS5FL first heavy chain, C214 of a first YS5FL light chain, C219 of a YS5FL second heavy chain, and C214 of a second YS5FL light chain. In some embodiments, an anti-CD46 immunoconjugate comprises two YS5FL heavy chains and an effector-linker complex is conjugated to C225 of a first YS5FL heavy chain and C225 of a second YS5FL heavy chain. In some embodiments, an anti-CD46 immunoconjugate comprises two YS5FL heavy chains and an effector-linker complex is conjugated to C228 of a first YS5FL heavy chain and C228 of a second YS5FL heavy chain. In some embodiments, an immunoconjugate comprises two, four, six, or eight effectors and the effectors are conjugated to any one, two, three, or four, respectively, of the following pairs of cysteines: C219 of HC1 and C214 of LC1; C219 of HC2 and C214 of LC2; C225 of HC1 and C225 of HC2; and C228 of HC1 and C228 of HC2.

Immunoconjugate Binding to Target Cells and Activity on Target Cells

[00118] In some embodiments, an anti-CD46 antibody or immunoconjugate described herein binds to CD46 expressed on the surface of a target cell (e.g., a cancer cell) and is internalized by the cell. In some embodiments, the antibody or immunoconjugate is internalized into the target cell via macropinocytosis. In some embodiments, the antibody or immunoconjugate is targeted to a lysosome of the cell upon internalization. In some embodiments, the antibody or immunoconjugate induces internalization into the cell without crosslinking.

[00119] In some embodiments, an anti-CD46 antibody or immunoconjugate described herein mediates killing of a target cell (e.g., cancer cell) upon internalization. In some embodiments, the anti-CD46 antibody or immunoconjugate induces apoptosis of the target cell (e.g., cancer cell) upon internalization. In some embodiments, the anti-CD46 antibody or immunoconjugate inhibits cell division of the target cell (e.g., cancer cell) upon internalization. In some embodiments, the anti-CD46 antibody or immunoconjugate selectively inhibits cell division of cancer cells upon internalization and does not inhibit cell division of non-cancer cells upon internalization.

Production of Antibodies or Antigen Binding Fragments Thereof

[00120] In some embodiments, antibodies (and antigen binding fragment thereof) are produced using any method known in the art to be useful for the synthesis of antibodies, in particular, by chemical synthesis or by recombinant expression techniques.

[00121] In some embodiments, an antibody (or antigen binding fragment thereof) is expressed recombinantly. In some embodiment, the nucleic acid encoding the antibody (or antigen binding fragment thereof) is assembled from chemically synthesized oligonucleotides. In some embodiments, a nucleic acid molecule encoding an antibody is generated from a suitable source (e.g., an antibody cDNA library, or cDNA library generated from any tissue or cells expressing the immunoglobulin) by PCR amplification using synthetic primers hybridizable to the 3′ and 5′ ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence.

[00122] In some embodiments, an antibody (or antigen binding fragment thereof) is made by immunizing an animal, such as a mouse, to generate polyclonal or monoclonal antibodies.

[00123] In some embodiments, an expression vector comprising the nucleotide sequence of an antibody or the nucleotide sequence of an antibody is transferred to a host cell by conventional techniques (e.g., electroporation, liposomal transfection, and calcium phosphate precipitation), and the transfected cells are then cultured by conventional techniques to produce the antibody. In some embodiments, the expression of the antibody is regulated by a constitutive, an inducible or a tissue, specific promoter.

[00124] A variety of host-expression vector systems can be utilized to express an antibody (or antigen binding fragment thereof) described herein. These include, but are not limited to, microorganisms such as bacteria (e.g., E. coli and B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing an antibody or its binding fragment coding sequences; yeast (e.g., Saccharomyces Pichia) transformed with recombinant yeast expression vectors containing an antibody or its binding fragment coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing an antibody or its binding fragment coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus (CaMV) and tobacco mosaic virus (TMV)) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing an antibody or its binding fragment coding sequences; or mammalian cell systems (e.g., COS, CHO, BH, 293, 293T, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g. the adenovirus late promoter; the vaccinia virus 7.5K promoter).

[00125] For long-term, high-yield production of recombinant proteins, stable expression may be preferred. In some embodiments, cell lines that stably express an antibody are made. Following the introduction of the foreign DNA, engineered cells are then allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. A selectable marker in the recombinant plasmid may be used to confer resistance to the selection.

[00126] In some embodiments, any method known in the art for purification of an antibody can be used, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins.

Expression Vectors

[00127] Vectors can include any suitable vector derived from either a eukaryotic or prokaryotic sources. In some cases, vectors are obtained from bacteria (e.g. E. coli), insects, yeast (e.g. Pichia pastoris), algae, or mammalian sources. Exemplary bacterial vectors include pACYC177, pASK75, pBAD vector series, pBADM vector series, pET vector series, pETM vector series, pGEX vector series, pHAT, pHAT2, pMal-c2, pMal-p2, pQE vector series, pRSET A, pRSET B, pRSET C, pTrcHis2 series, pZA31-Luc, pZE21-MCS-1, pFLAG ATS, pFLAG CTS, pFLAG MAC, pFLAG Shift-12c, pTAC-MAT-1, pFLAG CTC, or pTAC-MAT-2.

[00128] Exemplary insect vectors include pFastBac1, pFastBac DUAL, pFastBac ET, pFastBac HTa, pFastBac HTb, pFastBac HTc, pFastBac M30a, pFastBact M30b, pFastBac, M30c, pVL1392, pVL1393, pVL1393 M10, pVL1393 M11, pVL1393 M12, FLAG vectors such as pPolh-FLAG1 or pPolh-MAT 2, or MAT vectors such as pPolh-MAT1, or pPolh-MAT2.

[00129] In some cases, yeast vectors include Gateway® pDEST™ 14 vector, Gateway® pDEST™ 15 vector, Gateway® pDEST™ 17 vector, Gateway® pDEST™ 24 vector, Gateway® pYES-DEST52 vector, pBAD-DEST49 Gateway® destination vector, pAO815 Pichia vector, pFLD1 Pichi pastoris vector, pGAPZA,B, & C Pichia pastoris vector, pPIC3.5K Pichia vector, pPIC6 A, B, & C Pichia vector, pPIC9K Pichia vector, pTEF1/Zeo, pYES2 yeast vector, pYES2/CT yeast vector, pYES2/NT A, B, & C yeast vector, or pYES3/CT yeast vector.

[00130] Exemplary algae vectors include pChlamy-4, vector or MCS vector.

[00131] Examples of mammalian vectors include transient expression vectors or stable expression vectors. Mammalian transient expression vectors may include pRK5, p3xFLAG-CMV 8, pFLAG-Myc-CMV 19, pFLAG-Myc-CMV 23, pFLAG-CMV 2, pFLAG-CMV 6a,b,c, pFLAG-CMV 5.1, pFLAG-CMV 5a,b,c, p3xFLAG-CMV 7.1, pFLAG-CMV 20, p3xFLAG-Myc-CMV 24, pCMV-FLAG-MAT1, pCMV-FLAG-MAT2, pBICEP-CMV 3, or pBICEP-CMV 4. Mammalian stable expression vector may include pFLAG-CMV 3, p3xFLAG-CMV 9, p3xFLAG-CMV 13, pFLAG-

Myc-CMV 21, p3xFLAG-Myc-CMV 25, pFLAG-CMV 4, p3xFLAG-CMV 10, p3xFLAG-CMV 14, pFLAG-Myc-CMV 22, p3xFLAG-Myc-CMV 26, pBICEP-CMV 1, or pBICEP-CMV 2.

[00132] In some instances, a cell-free system is a mixture of cytoplasmic and/or nuclear components from a cell and is used for in vitro nucleic acid synthesis. In some cases, a cell-free system utilizes either prokaryotic cell components or eukaryotic cell components. Sometimes, a nucleic acid synthesis is obtained in a cell-free system based on for example Drosophila cell, Xenopus egg, or HeLa cells. Exemplary cell-free systems include, but are not limited to, E. coli S30 Extract system, E. coli T7 S30 system, or PURExpress®.

Host Cells

[00133] A host cell can be any suitable cell such as a naturally derived cell or a genetically modified cell. In some instances, a host cell is a production host cell. In some instances, a host cell is a eukaryotic cell. In other instances, a host cell is a prokaryotic cell. In some cases, a eukaryotic cell includes fungi (e.g., yeast cells), animal cell, or plant cell. In some cases, a prokaryotic cell is a bacterial cell. Examples of bacterial cell include gram-positive bacteria or gram-negative bacteria. Sometimes the gram-negative bacteria is anaerobic, rod-shaped, or both.

[00134] In some instances, gram-positive bacteria include Actinobacteria, Firmicutes, or Tenericutes. In some cases, gram-negative bacteria include Aquificae, Deinococcus-Thermus, Fibrobacteres–Chlorobi/Bacteroidetes (FCB group), Fusobacteria, Gemmatimonadetes, Nitrospirae, Planctomycetes–Verrucomicrobia/ Chlamydiae (PVC group), Proteobacteria, Spirochaetes or Synergistetes. Other bacteria can be Acidobacteria, Chloroflexi, Chrysiogenetes, Cyanobacteria, Deferribacteres, Dictyoglomi, Thermodesulfobacteria, or Thermotogae. A bacterial cell can be Escherichia coli, Clostridium botulinum, or Coli bacilli.

[00135] Exemplary prokaryotic host cells include, but are not limited to, BL21, Mach1™, DH10B™, TOP10, DH5α, DH10Bac™, OmniMax™, MegaX™, DH12S™, INV110, TOP10F', INVαF, TOP10/P3, ccdB Survival, PIR1, PIR2, Stbl2™, Stbl3™, or Stbl4™.

[00136] In some instances, animal cells include a cell from a vertebrate or from an invertebrate. In some cases, an animal cell includes a cell from a marine invertebrate, fish, insects, amphibian, reptile, or mammal. In some cases, a fungus cell includes a yeast cell, such as brewer's yeast, baker's yeast, or wine yeast.

[00137] Fungi include ascomycetes such as yeast, mold, filamentous fungi, basidiomycetes, or zygomycetes. In some instances, yeast includes Ascomycota or Basidiomycota. In some cases, Ascomycota includes Saccharomycotina (true yeasts, e.g. Saccharomyces cerevisiae (baker's yeast)) or Taphrinomycotina (e.g. Schizosaccharomycetes (fission yeasts)). In some cases,

Basidiomycota includes Agaricomycotina (e.g. Tremellomycetes) or Pucciniomycotina (e.g. Microbotryomycetes).

[00138] Exemplary yeast or filamentous fungi include, for example, the genus: Saccharomyces, Schizosaccharomyces, Candida, Pichia, Hansenula, Kluyveromyces, Zygosaccharomyces, Yarrowia, Trichosporon, Rhodosporidi, Aspergillus, Fusarium, or Trichoderma. Exemplary yeast or filamentous fungi include, for example, the species: Saccharomyces cerevisiae, Schizosaccharomyces pombe, Candida utilis, Candida boidini, Candida albicans, Candida tropicalis, Candida stellatoidea, Candida glabrata, Candida krusei, Candida parapsilosis, Candida guilliermondii, Candida viswanathii, Candida lusitaniae, Rhodotorula mucilaginosa, Pichia metanolica, Pichia angusta, Pichia pastoris, Pichia anomala, Hansenula polymorpha, Kluyveromyces lactis, Zygosaccharomyces rouxii, Yarrowia lipolytica, Trichosporon pullulans, Rhodosporidium toru-Aspergillus niger, Aspergillus nidulans, Aspergillus awamori, Aspergillus oryzae, Trichoderma reesei, Yarrowia lipolytica, Brettanomyces bruxellensis, Candida stellata, Schizosaccharomyces pombe, Torulaspora delbrueckii, Zygosaccharomyces bailii, Cryptococcus neoformans, Cryptococcus gattii, or Saccharomyces boulardii.

[00139] Exemplary yeast host cells include, but are not limited to, Pichia pastoris yeast strains such as GS115, KM71H, SMD1168, SMD1168H, and X-33; and Saccharomyces cerevisiae yeast strain such as INVSc1.

[00140] In some instances, additional animal cells include cells obtained from a mollusk, arthropod, annelid, or sponge. In some cases, an additional animal cell is a mammalian cell, e.g., from a primate, ape, equine, bovine, porcine, canine, feline or rodent. In some cases, a rodent includes mouse, rat, hamster, gerbil, hamster, chinchilla, fancy rat, or guinea pig.

[00141] Exemplary mammalian host cells include, but are not limited to, 293A cell line, 293FT cell line, 293F cells , 293 H cells, CHO DG44 cells, CHO-S cells, CHO-K1 cells, FUT8 KO CHOK1, Expi293F™ cells, Flp-In™ T-REx™ 293 cell line, Flp-In™-293 cell line, Flp-In™-3T3 cell line, Flp-In™-BHK cell line, Flp-In™-CHO cell line, Flp-In™-CV-1 cell line, Flp-In™-Jurkat cell line, FreeStyle™ 293-F cells, FreeStyle™ CHO-S cells, GripTite™ 293 MSR cell line, GS-CHO cell line, HepaRG™ cells, T-REx™ Jurkat cell line, Per.C6 cells, T-REx™-293 cell line, T-REx™-CHO cell line, and T-REx™-HeLa cell line.

[00142] In some instances, a mammalian host cell is a stable cell line, or a cell line that has incorporated a genetic material of interest into its own genome and has the capability to express the product of the genetic material after many generations of cell division. In some cases, a mammalian host cell is a transient cell line, or a cell line that has not incorporated a genetic material of interest into its own genome and does not have the capability to express the product of the genetic material after many generations of cell division.

[00143] Exemplary insect host cells include, but are not limited to, Drosophila S2 cells, Sf9 cells, Sf21 cells, High Five™ cells, and expresSF+® cells.

[00144] In some instances, plant cells include a cell from algae. Exemplary insect cell lines include, but are not limited to, strains from Chlamydomonas reinhardtii 137c, or Synechococcus elongatus PPC 7942.

Therapeutic Methods

[00145] In one aspect, provided herein are methods of treating cancer by administering an anti-CD46 antibody or immunoconjugate described herein.

[00146] In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is relapsing multiple myeloma. In some embodiments, the cancer is remitting multiple myeloma. In some embodiments, the cancer is relapsing or remitting multiple myeloma.

[00147] In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is castration resistant prostate cancer. In some embodiments, the cancer is metastatic prostate cancer.

[00148] In one aspect, provided herein are anti-CD46 antibodies or immunoconjugates described herein for use as a medicament are provided. In one aspect, provided herein are anti-CD46 antibodies or immunoconjugates described herein for use in treating a disease, in particular for use in the treatment of cancer, are provided. In one aspect, provided herein are anti-CD46 antibodies or immunoconjugates described herein for use in a method of treating cancer are provided. In one aspect, provided herein are anti-CD46 antibodies or immunoconjugates described herein for use in the treatment of a disease in an individual in need thereof. In one aspect, provided herein are anti-CD46 antibodies or immunoconjugates described herein for use in a method of treating an individual having cancer comprising administering to the individual a therapeutically effective amount of anti-CD46 antibodies or immunoconjugates described herein. In one aspect, provided herein are anti-CD46 antibodies or immunoconjugates described herein before in the manufacture or preparation of a medicament for the treatment of a disease in an individual in need thereof. In one aspect, provided herein are the medicament is for use in a method of treating a cancer comprising administering to an individual having cancer a therapeutically effective amount of the medicament.

Dosing and Administration

[00149] For use in therapeutic methods, anti-CD46 antibodies or immunoconjugates described herein can be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the

disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

[00150] In some embodiments, an antibody or immunoconjugate described herein is administered to a human subject via intravenous infusion. In some embodiments, the antibody or immunoconjugate is administered to a human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days. In some embodiments, the antibody or immunoconjugate is administered to a human subject every 21 days.

[00151] In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose from about 1.0 to about 5.0 mg/kg. In some embodiments, the antibody or immunoconjugate to 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. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose from about 1.5 to about 2.5 mg/kg. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose from about 1.2 to about 3.0 mg/kg.

[00152] In some embodiments, the antibody or immunoconjugate is administered to a human subject 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. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose of about 1.8, about 2.4, about 2.7, about 3.0, or about 3.2 mg/kg. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose of about 1.8 mg/kg. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose of about 2.4 mg/kg. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose of about 2.7 mg/kg. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose of about 3.0 mg/kg. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose of about 3.2 mg/kg. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose of about 1.5 mg/kg. In some embodiments, the antibody or

immunoconjugate is administered to a human subject at a dose of about 2.5 mg/kg. In some embodiments, the antibody or immunoconjugate is administered to a human subject at a dose of about 3.0 mg/kg. In some embodiments, weight is measured in kg. In some embodiments, the weight of the human subject is an actual body weight. In some embodiments, weight is measured in kg. In some embodiments, the weight of the human subject is an adjusted body weight (AJBW).

Determining CD46 expression

[00153] In one aspect, provided herein are methods of treating a cancer in a subject by (1) determining that the cancer comprises CD46, and (2) administering an anti-CD46 antibody or immunoconjugate described herein. In some embodiments, a cancer that expresses CD46 is sensitive to treatment by the anti-CD46 antibody or immunoconjugate. In some embodiments, the anti-CD46 antibody or immunoconjugate is a more effective anti-cancer agent when the cancer expresses CD46 or expresses higher levels of CD46 than non-cancerous control. In some embodiments, the non-cancerous control is a matched non-cancer control tissue from the subject or an individual without cancer. For example, if the cancer is a prostate cancer, the non-cancer control tissue may be a healthy prostate.

[00154] In some embodiments, an anti-CD46 antibody is used to determine CD46 expression by the cancer. CD46 expression by a cancer (e.g. a cancer cell, a cancerous lesion, a metastatic cell) may be detected by various methods such as immunofluorescence microscopy, immunohistochemistry, or flow cytometry.

[00155] In another embodiment, the copy number of the CD46 gene is determined in the cancer. The CD46 gene is localized on the q arm of chromosome 1 at band 32 (1q32). In some embodiments, a 1q amplification indicates that CD46 is more highly expressed. In some embodiments, the 1q amplification comprises an amplification of 1q32. In some embodiments, the 1q amplification comprises an amplification of 1q21, and amplification of 1q32 is inferred from the amplification of 1q21. In some embodiments, the gene amplification comprises an increase in the copy number of the CD46 gene. In some embodiments, the copy number of the CD46 gene is 3 or more. In some embodiments, the copy number of the CD46 gene is 4, 5, 6, 7, or 8.

Pharmaceutical Compositions and Formulations

[00156] In a further aspect, the invention provides pharmaceutical compositions comprising an anti-CD46 antibody or immunoconjugate described herein, e.g., for use in any of the above therapeutic methods. In one embodiment, the pharmaceutical composition comprises an anti-CD46 antibody or immunoconjugate provided herein and at least one pharmaceutically acceptable

excipient. The preparation of a pharmaceutical composition that contains an anti-CD46 antibody or immunoconjugate described herein will be known to those of skill in the art in light of the present disclosure, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, incorporated by reference herein.

[00157] In some embodiments, the pharmaceutical composition comprises a buffer. In some embodiments, the buffer comprises histidine. In some embodiments, the pharmaceutical composition comprises from about 10 to about 40 mM, about 10 to about 30 mM, or about 10 to about 20 mM histidine buffer. In some embodiments, the pharmaceutical composition comprises about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35 mM, or about 40 mM histidine buffer. In some embodiments, the pharmaceutical composition comprises about 20 mM histidine buffer.

[00158] In some embodiments, the pharmaceutical composition comprises a cryoprotectant. In some em-bodiments, the cryoprotectant comprises a saccharide. In some embodiments, the cryoprotectant comprises sucrose or trehalose. In some embodiments, the cryoprotectant comprises sucrose. In some embodiments, the pharmaceutical composition comprises from about 4% to about 12%, about 4% to about 11%, about 4% to about 10%, about 4% to about 9%, about 4% to about 8%, about 5% to about 12%, about 5% to about 11%, about 5% to about 10%, about 5% to about 9%, about 5% to about 8%, about 6% to about 12%, about 6% to about 11%, about 6% to about 10%, about 6% to about 9%, about 6% to about 8%, about 7% to about 12%, about 7% to about 11%, about 7% to about 10%, about 7% to about 9%, or about 7% to about 8% sucrose. In some embodiments, the pharmaceutical composition comprises about 8% sucrose.

[00159] In some embodiments, the pharmaceutical composition comprises a stabilizing agent. In some embodiments, the stabilizing agent prevents denaturation of said recombinant antibody, prevents aggregation of said immunoconjugates, or both. In some embodiments, the stabilizing agent is a polysorbate. In some embodiments, the stabilizing agent is polysorbate 20. In some embodiments, the stabilizing agent is polysorbate 80. In some embodiments, the pharmaceutical composition comprises a polysorbate (e.g., polysorbate 80) from about 0.001% to 0.1%, 0.001% to 0.05%, 0.001% to 0.04%, 0.001% to 0.03%, 0.001% to 0.02%, or 0.001% to 0.01%. In some embodiments, the pharmaceutical composition comprises a polysorbate (e.g., polysorbate 80) at about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1%. In some embodiments, the pharmaceutical composition comprises a polysorbate (e.g., polysorbate 80) at about 0.01%.

[00160] In some embodiments, the pharmaceutical composition has a pH of from about 5.0 to about 7.0. In some embodiments, the pharmaceutical composition has a pH of about 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5. In some embodiments, the pharmaceutical composition has a pH of about 6.0.

[00161] In some embodiments, pharmaceutical composition comprises an anti-CD46 antibody or immunoconjugate described herein at a concentration from about 5.0 mg/ml to 15.0 mg/ml, 5.0 mg/ml to 14.0 mg/ml, 5.0 mg/ml to 13.0 mg/ml, 5.0 mg/ml to 12.0 mg/ml, 5.0 mg/ml to 11.0 mg/ml, 5.0 mg/ml to 10.0 mg/ml, 6.0 mg/ml to 15.0 mg/ml, 7.0 mg/ml to 15.0 mg/ml, 8.0 mg/ml to 15.0 mg/ml, 9.0 mg/ml to 15.0 mg/ml, or 10.0 mg/ml to 15.0 mg/ml. In some embodiments, pharmaceutical composition comprises an anti-CD46 antibody or immunoconjugate described herein at a concentration of about 5.0 mg/ml, 6.0 mg/ml, 7.0 mg/ml, 8.0 mg/ml, 9.0 mg/ml, 10.0 mg/ml, 11.0 mg/ml, 12.0 mg/ml, 13.0 mg/ml, 14.0 mg/ml, or 15.0 mg/ml. In some embodiments, the pharmaceutical composition comprises an anti-CD46 antibody or immunoconjugate described herein at a concentration of about 5.0 mg/ml ± 1.0 mg/mL, 6.0 mg/ml ± 1.0 mg/mL, 7.0 mg/ml ± 1.0 mg/mL, 8.0 mg/ml ± 1.0 mg/mL, 9.0 mg/ml ± 1.0 mg/mL, 10.0 mg/ml ± 1.0 mg/mL, 11.0 mg/ml ± 1.0 mg/mL, 12.0 mg/ml ± 1.0 mg/mL, 13.0 mg/ml ± 1.0 mg/mL, 14.0 mg/ml ± 1.0 mg/mL, or 15.0 mg/ml ± 1.0 mg/mL. In some embodiments, the pharmaceutical composition comprises an anti-CD46 antibody or immunoconjugate described herein at a concentration of about 10.0 mg/ml ± 1.0 mg/mL.

Exemplary Formulation

[00162] An exemplary formulation of an anti-CD46 antibody or immunoconjugate described herein comprises about an anti-CD46 antibody or immunoconjugate described herein at a concentration of about 10.0 mg/ml ± 1.0 mg/mL; about 20 mM histidine buffer, about 8.0% sucrose, about 0.01% polysorbate 80, pH 6.0.

Articles of Manufacture

[00163] In another aspect of the invention, an article of manufacture containing materials useful for the treatment of cancers described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper that is pierceable by a hypodermic injection needle).

[00164] The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises the bispecific antibody of the invention; and (b) a second container with a composition contained therein, wherein the

composition comprises a further cytotoxic or otherwise therapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition.

[00165] Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

EXAMPLES

[00166] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1: YS5FL binding to the surface of cancer cells

[00167] Cell surface CD46 was detected by flow cytometry. Cells were harvested, centrifuged and resuspended in FACS buffer (PBS + 2% FBS) at a concentration of $1x10^6$ cells/mL. 100 μL of cell suspension was dispensed into each well of a 96-well plate, 100 μL of YS5FL at 10 μg/mL was added to the wells and incubated for 1 hour at 4 °C. The cells were washed three times with FACS buffer. After the third wash, the cells were resuspended in 100 μL 1: 500 diluted AlexaFluor-488 mouse anti-Human IgG1 Fc secondary antibody and incubated for 1 hour at 4 °C in the dark. The cells were washed three times with 200 μL PBS by centrifuging at 2000 RPM for 5 minutes. After the last wash, the cells were resuspended in 300 μL cold PBS and analyzed on a FACSVerse™ (BD Biosciences) flow cytometer. YS5FL bound specifically to the surface of LnCap-C4-2B, LnCap-C4, DU145, PC3-luc, and Hs27 prostate cancer cells, but not to non-tumor BPH1 cells. **FIG. 1**. Likewise, YS5FL bound specifically to the surface of RPMI8226, MM.1S, MM.1R, and INA6 multiple myeloma cells. **FIG. 2**.

Example 2: Preparation of the FOR46 immunoconjugate

[00168] The structure of YS5FL conjugated to an MMAE effector via a mc-vc-PAB linker is shown in **FIG. 3**. Purified YS5FL mAb (10 mg/ml) is adjusted to a pH of 6.8 with sodium phosphate buffer and then treated with TCEP (TCEP/mAb ratio of 2.1) for two hours at 22°C. Reduced mAb is reacted with mc-vc-PAB-MMAE (drug/mAb ratio of 6) in 9% dimethylacetamide for 15 min. The mAb is reduced a second time for one hour, conjugated a second time for 60 min, and the reaction is quenched by lowering the pH to 5.0 with 1M acetic acid, yielding a FOR46 immunoconjugate with a drug to antibody ratio of about 3.7, as determined by hydrophobic interaction chromatography. **FIG. 4**.

Example 3: FOR46 drug product

[00169] The FOR46 immunoconjugate was formulated into a drug product such that it could be administered to a human subject. The formulation contains 10.0 ± 1.0 mg/mL FOR46 drug substance; 20 mM L-histidine buffer, 8.0% (w/v) sucrose, and 0.01% (w/v) polysorbate 80, pH 6.0. The formulation was determined to provide adequate stability (prevention of denaturation of the antibody and prevention of aggregation), buffering, and cryoprotection for storage at -20°C. After storage for 1 month at 5°C, the formulation retained >90% binding potency and cell based activity; was >90% monomeric; had residual MMAE of <15 μg/mL; and was essentially free of visible particles.

Example 4: Dose escalation study - treatment of metastatic castration resistant prostate cancer with FOR46

[00170] A dose escalation clinical trial is being carried out to determine the maximum tolerated dose (or maximum tested dose) of FOR46 in human subjects having metastatic castration resistant prostate cancer (mCRPC), including treatment associated small cell / neuroendocrine prostate cancer (tSCNC). Eligible patients had progressed on 1 or more androgen signaling inhibitor(s), exhibited maintained castrate testosterone levels (< 50 ng/dL); and exhibited organ function defined by the following hemoglobin (Hgb) > 8 g/dL, absolute neutrophil count (ANC) > 1500/μL; platelets (Plts) > 100k; aspartate transaminase to alanine transaminase ratio (ALT/AST) < 2.5 x upper limit of normal (ULN); bilirubin (Bili) < 1.5 mg/dL; and creatinine < 1.5 x ULN. No prior chemotherapy for mCRPC was allowed. Eligible patients received or are contemplated to receive FOR46 via IV infusion every 21 days. Thirty-three subjects were enrolled at 10 dose levels from 0.1 to 3.0 mg/kg. The median age was 66 (range 42 – 81); median baseline PSA was 41 (range 0.2 - 1627); and 7 subjects had visceral organ metastases. Patient demographics are presented in Table 7.

Table 7. Demographics of patients in the prostate cancer dose escalation trial.

Characteristic (N = 33)	**Current Data**
Median age (range)	67.5 (42-81)
Gender	33 Males
Race – White/Asian/Other/Black/American Indian	26/1/1/4/1
Median number of prior regimens (range)	3 (2-8)
Type of disease progression at study entry PSA Nodal only (no bone disease) Bone (± nodal disease) Visceral (lung, liver, adrenal, CNS) disease ± other sites	 13 3 16 4
Number of patients with visceral disease	7

[00171] An accelerated titration followed by 3+3 dose escalation design was used. Following excess toxicity (neutropenia and fatigue) in subjects with high body mass index (BMI), dosing was changed from actual body weight to adjusted body weight. G-CSF secondary prophylaxis was specified for subjects experiencing grade ≥ 3 neutropenia during a previous treatment cycle. In the absence of excess toxicity, treatment is continued if the investigator determines there is potential clinical benefit. A 50% decrease in serum prostate specific antigen (PSA) levels provides preliminary objective evidence of a response to treatment.

[00172] The 33 subjects were grouped into 10 cohorts receiving different doses. The cohorts and patient status are summarized in **Table 8**. Reductions in PSA and tumor burden are summarized in **Table 9**. At 1.2 mg/kg or higher (n = 24), 9 subjects (38%) had a 50% reduction in PSA levels (PSA50 response), and 15 (63%) had any decline in PSA. Of 8 subjects with measurable disease, three objective partial responses (PR) were reported, and 6 had stable disease lasting from 9 to 39 weeks, as determined by RECIST criteria. Eisenhauer et al, New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), European Journal of Cancer 45 (2009) 228-249. The median number of treatment cycles is 6 (range 1 - 28) with 11 ongoing.

[00173] PSA levels and RECIST results after each infusion cycle are presented for Cohorts 4-10 are presented in **Tables 10-16**, respectively. The results for all patients are summarized in **FIG. 6**.

[00174] Patient 12 had the most substantial reduction in tumor burden. A CT scan after three cycles of treatment with 2.7 mg/kg revealed complete shrinkage of the largest tumor. **FIG. 5A**. The sum of the largest diameters of the target lesions (SLD, including lung nodules and a peri-rectal soft tissue mass) was reduced from 5.7 cm at baseline to 2.0 cm (a 65% reduction) after cycle 6. This was accompanied by a 71% reduction in serum PSA and a decrease in non-target lesions including RP nodes. **FIG. 5B**.

[00175] Neutropenia was analyzed by determining an absolute neutrophil count (ANC) as shown in **Table 17**. Grade 2 or higher neutropenia was observed in 12 of 16 patients treated with at least 1.8 mg/kg FOR46.

Table 8. Cohorts, Patient ID's and current status of subject in the prostate cancer dose escalation trial. EOT: end of treatment; C: course; D: day; * dose increase to 2.1 mg/kg.

	Patient ID	Status
Cohort 4 (1.2 mg/kg)	003-04-008	EOT due to disease progression (C9) after COVID-19 treatment pause
	004-04-009*	Ongoing C26D1
	001-04-010	EOT due to disease progression (C3)
Cohort 5 (1.8 mg/kg)	004-05-011	EOT due to disease progression (C13)
	001-05-012	EOT due to disease progression (C3)
	004-05-013	EOT due to increased neuropathy (C11)
	004-05-014*	EOT due to disease progression (C15)
	002-05-015	EOT due to disease progression (C5)
	004-05-016	EOT due to disease progression (C9)
	004-05-017	EOT due to increased neuropathy (C10)
Cohort 6 (2.4 mg/kg)	001-06-018	Ongoing C17D1
	004-06-019	EOT due to disease progression (C6)
	004-06-020	Pt deceased prior to C2D1 – Not evaluable for response
Cohort 7 (2.1 mg/kg)	004-07-021	EOT due to disease progression (C3)
	003-07-022	EOT due to disease progression (C3)
	003-07-023	EOT patient withdrawn (C1) - axillary adenopathy; RUE swelling
Cohort 8 (2.4 mg/kg w/AJBW)	001-08-024	EOT due to disease progression (C9)
	004-08-025	EOT due to disease progression (C10)
	001-08-026	Ongoing C10D1 – no dose reduction through C10 (165 mg)
	001-08-027	Ongoing C9D1 – no dose reduction through C9 (191 mg)
Cohort 9 (2.7 mg/kg) AJBW	001-09-028	Ongoing C7D1 – no dose reduction through C7 (183 mg)
	005-09-029	Ongoing C5D1 – dose reduced to 2.4mg/kg at C2 and 1.8 mg/kg at C3
	004-09-030	Ongoing C6D1 – no dose reduction through C6 (173.9 mg)
Cohort 10 (3.0 mg/kg) AJBW	003-10-031	C4D1 – C2 dose reduced to 2.4 mg/kg; C3 dose reduced to 2.1 mg/kg C4 delayed due to colitis and dose reduced to 1.8 mg/kg
	004-10-032	Death due to disease progression (C1)
	001-10-033	C3D1 – dose reduced to 2.7 mg/kg
Dose Expansion	003-09-101	C1D1

Table 9. Summary of responses to FOR46 in the prostate cancer dose escalation trial. PR: partial response

Patient ID	Dose (mg/kg)	% PSA Change	PSA Change	RECIST	# Cycles
003-04-008	1.2	+37			9
004-04-009	1.2	-94	≥50%		26+
001-04-010	1.2	-51	≥50%		3
004-05-011	1.8	+75			14
001-05-012	1.8	+34			3
004-05-013	1.8	-56	≥50%		13
004-05-014	1.8	-31	Red		14
002-05-015	1.8	-14	Red		2
004-05-016	1.8	-50	≥50%		9
004-05-017	1.8	-79	≥50%		9
001-06-018	2.4	-51	≥50%		18+
004-06-019	2.4	+76			6
004-07-021	2.1	+55			3
003-07-022	2.1	-34	Red		5
001-08-024	2.4 AJBW	-12	Red		9
004-08.025	2.4 AJBW	+27			10
001-08-026	2.4 AJBW	-3	Red		4
001-08-027	2.4 AJBW	+20			9
001-09-028	2.7 AJBW	-71	≥50%	PR	10+
004-09-030	2.7 AJBW	-79	≥50%		7+
003-10-031	3.0 AJBW	34		PR	4+
001-10-033	3.0 AJBW	-74	≥50%	PR	4+

Table 10. Serum PSA (mg/ml) levels and tumor dimensions (RECIST) in Cohort 4 metastatic castration resistant prostate cancer patients treated with 1.2 mg/kg FOR46. SCR: screen; C: course; D: day; N/N: Non-complete response, non-progressive disease; SD: stable disease; PD: progressive disease; * dose increased to 2.1 mg/kg AJBW at C17.

Patient ID	SCR	C1	C2	C3	C4	C7	C10	C14	C18	C22	C26
003-04-008 RECIST	399 98 mm	352.9	419.3	414.2	484.0 SD -6.1% 92 mm	507 SD -9.8% 88 mm	EOT PD	--	--	--	
004-04-009* RECIST	78.7 NM	9.4	2.4	0.58	0.66 N/N	1.17 N/N	4.13 N/N	10.4 N/N	14.2 N/N	17.37 N/N	19.33 N/N
001-04-010 RECIST	1603 18mm	1626	>149	794.6	1502 PD	--	--	--	--		

Table 11 (part 1). Serum PSA (mg/ml) levels and tumor dimensions (RECIST) in Cohort 5 metastatic castration resistant prostate cancer patients treated with 1.8 mg/kg FOR46. SCR: screen; C: course; D: day; SD: stable disease; PD: progressive disease; *004-05-014 discontinued after cycle 15 due to peripheral neuropathy and fatigue/weakness; AE: adverse event.

Patient ID	SCR	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
004-05-011 RECIST	45.6 43	55.0	78.8	95.0	96.1 SD 47	98.9	126.7	146.4 SD 51	163.5	171.5	221 SD 52
001-05-012 RECIST	382 134	545. 5	623.6	731.8	1027 PD 174	--	--	--	--	--	--
004-05-013 RECIST	57.7 63	57.5	28.4	25.4	26.6 SD -14.2% 54	31.6	42.2	59.0 SD -9.5% 57	66.2	55.0	53.4 SD -6.77% 59
004-05-014 RECIST	129 40	152. 7	198.4	141.1	150.1 SD -7.5% 37	109	106.2	111 SD -17.5% 33	113.9	104.9	127.7 SD -14.2% 35
002-05-015 RECIST	685 NM	884	758	991	1179 N/N	1136	1147	--	--	--	--
004-05-016 RECIST	91.2 NM	71.5	81.7	54.6	49.1 N/N	35.7	48	54.8 N/N	54.7	77.5	99.1 PD new lesion
004-05-017 RECIST	1.49 NM	1.44	0.8	0.66	1.0 N/N	0.4	0.3	0.3 N/N	0.4	0.73	1.8 EOT N/N

Table 11 (continued). Serum PSA (mg/ml) levels and tumor dimensions (RECIST) in Cohort 5 metastatic castration resistant prostate cancer patients treated with 1.8 mg/kg FOR46. C: course; D: day; SD: stable disease; PD: progressive disease; *004-05-014 discontinued after cycle 15 due to peripheral neuropathy and fatigue/weakness; AE: adverse event.

Patient ID	C11	C12	C13	C14	C15
004-05-011 RECIST	235	254	250.8	312.6 53	--
001-05-012 RECIST	--	--	--	--	--
004-05-013 RECIST	60.6	48.27	53.79	64.27 PD	--
004-05-014 RECIST	135.5	173.3	212.5	256.9 SD -17.5% 33	297.3 Off due to AE*
002-05-015 RECIST					
004-05-016 RECIST					
004-05-017 RECIST					

Table 12. Serum PSA (mg/ml) levels and tumor dimensions (RECIST) in Cohort 6 metastatic castration resistant prostate cancer patients treated with 2.4 mg/kg FOR46. SCR: screen; C: course; D: day; SD: stable disease; N/N: Non-complete response, non-progressive disease; NE: inevaluable.

Patient ID	SCR	C1	C2	C3	C4	C5	C6	C7	C8
001-06-018* RECIST	47.6 NM	16.4	14.5	8.1	9.8 N/N	16.5	19.2	22.3 N/N	28.9
004-06-019* RECIST	3.53 NM	6.93	15.3	12.2	15.3 N/N	18.7	25.3	43.6	--
004-06-020 RECIST (mm)	7.5 179	5.6 NE	--	--	--	--	--	--	--

Patient ID	C9	C10	C11	C12	C13	C14	C15	C16	C17
001-06-018* RECIST	25.2	21.2 N/N	17.8	14.2	17.5	16.1 N/N	17.8	21.7	19.1
004-06-019* RECIST	--	--	--	--	--	--	--	--	
004-06-020 RECIST (mm)	--	--	--	--	--	--	--	--	

Table 13. Serum PSA (mg/ml) levels and tumor dimensions (RECIST) in Cohort 7 metastatic castration resistant prostate cancer patients treated with 2.1 mg/kg FOR46. SCR: screen; C: course; PD: progressive disease; NE: inevaluable; * Dose reduced from C2 on to 1.8 mg/kg actual body weight; # Dosed according to AJBW.

Patient ID	SCR	C1	C2	C3	C4	C5
004-07-021 RECIST	3.88 104	4.2	5.5	6.5	-- 113	--
003-07-022 RECIST (mm)	24.7 NM	34.1	31.4	27.7	20.7 PD	22.7
003-07-023# RECIST (mm)	119.5	138	487 NE	--	--	--

Table 14. Serum PSA (mg/ml) levels and tumor dimensions (RECIST) in Cohort 8 metastatic castration resistant prostate cancer patients treated with 2.4 mg/kg (adjusted body weight) FOR46. SCR: screen; C: course; NM: Not measurable; SD: Stable disease; N/N: Non-complete response, non-progressive disease.

Patient ID	SCR	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
001-08-024 RECIST	5.8 52 mm	5.8	5.1	5.3	5.9 SD 50 mm	7.1	9.5	13.5 SD 55 mm	14.2	15.2	21.75 PD 67 mm	
004-08-025 RECIST	164 61 mm	130	186	181	222 SD 63 mm	167	217	206 SD	229.8	250.5	301	357 EOT
001-08-026 RECIST	0.68 NM	0.62	0.60	0.64	0.75 N/N	0.98	1.4	0.7 N/N	2.1	1.6	1.921 N/N	
001-08-027 RECIST	82.6 NM	79.5	97.8	95.4	117 N/N	135	160	153.8 N/N	170.7	190.8		

Table 15. Serum PSA (mg/ml) levels and tumor dimensions (RECIST) in Cohort 9 metastatic castration resistant prostate cancer patients treated with 2.7 mg/kg (adjusted body weight) FOR46. SCR: screen; C: course; PR: partial response; NM: Not measurable; N/N: Non-complete response, non-progressive disease.

Patient ID	SCR	C1	C2	C3	C4	C5	C6	C7	C8
001-09-028 RECIST	22.4 57 mm	24.9	10.9	10.9	15.5 25 mm PR	31.0	33.97	54.5 20 mm PR	
005-09-029 RECIST	0.2 NM	0.20	0.21	0.20	0.20 N/N				
004-09-030 RECIST	134 NM	162	96	52	34.2 N/N	34.7	30.81		

Table 16. Serum PSA (mg/ml) levels and tumor dimensions (RECIST) in Cohort 10 metastatic castration resistant prostate cancer patients treated with 3.0 mg/kg (adjusted body weight) FOR46. SCR: screen; C: course; PR: partial response; D/C: discontinued care; *C2 dose reduced to 2.4 mg/kg (adjusted body weight); #C2 dose reduced to 2.7 mg/kg (adjusted body weight).

Patient ID	SCR	C1	C2	C3	C4
003-10-031* RECIST	5.80 24 mm	2.58	1.7	1.78	2.09 13 mm
004-10-032 RECIST	51.32	65.99	D/C Hospice		
001-10-033# RECIST	188.9 16 cm	221.6	65.4	57.3	50.8 8.5 cm PR

Table 17. Absolute neutrophil counts (x10^9/L) in metastatic castration resistant prostate cancer patients treated with FOR46. Neutropenia (^^ grade 2; ^^^ grade 3; ^^^^ grade 4); * G-CSF; ** adjusted body weight; *** adjusted body weight - did not receive full dose due to infusion reaction; D/C: discontinued care.

Patient ID	SCR	Wt	AJBW	Ht	BMI	Dose	C1D1	C1D8 or 9	C1D15	C2D1	C2D8	C2D15
001-06-018	6.54	114.7		185	33.5	275	2.83	^^^^0.19	^1.04	5.63	3.46	^^1.17
004-06-019	2.34	126.8		182.9	37.9	304.3	2.47	^^^^0.1*	--	2.37	4.6	4.1
004-06-020	7.00	123.6		177.8	39.1	296.6	4.86	^^^^0.21*	--	--	--	--
004-07-021	4.09	76.6		179.1	23.9	160.9	3.52	2.72	2.98	4.8	1.63	^^1.47
003-07-022	6.2	68		166	24.7	141.5	4.6	2.3	^^^0.7	6.4	13.7	7.0
003-07-023	8.0	112.4		180.3	34.6	189.2**	7.8	3.1	2.2	--	--	--
001-08-024	2.96	112.6		176.5	36.1	213***	2.60	2.47	3.31	1.98	2.61	1.93
004-08-025	4.43	71.7		169	25.1	172.6**	4.70	^^1.42	^^^^0.31	4.37	8.18	7.40
001-08-026	4.12	73.9		169.5	25.7	165**	2.28	^^1.11	^^1.31	3.81	^^1.16	^^^0.76
001-08-027	4.67	94.5		172.7	31.9	191**	3.60	2.39	3.45	4.88	3.40	3.95
001-09-028	2.53	75	68	167	26.9	183	2.50	^^^0.65	^^^0.70	2.80	5.50	4.29
005-09-029	10.68	90.9	80	178	28.7	217.1	4.98	^^^^0.39	3.23	10.90	1.95	^^^0.8
004-09-030	4.02	64.1	-	172.7	21.5	173.9	5.10	1.89	^^1.38	2.90	^^1.33	^^^^0.09
003-10-031	2.4	80.8	73	172.7	27.1	220.2	2.2	^^^^0.1	0.4	1.8	5.4	6.6
004-10-032	4.8	95.6	87	186.5	27.5	261	4.14	^^^^0.23 0.1 (Day 11)	D/C Hospice			
001-10-033	2.16	85.2		191.2	23.3	255	3.53	2.02 .895 (Day 6)	1.45	1.30	2.70	3.15
003-09-101	2.6	83		164.5	30.7	186.6	3.1					

[00176] Dose limiting toxicities were grade 4 neutropenia in 3 of 3 high body mass index (BMI) subjects at 2.4 mg/kg dosed by actual body weight and 2 of 3 subjects at 3.0 mg/kg dosed by adjusted body weight. The maximum tolerated dose (MTD) was 2.7 mg/kg by adjusted body weight (AJBW). The most common related adverse events were grade 4 neutropenia in 11 of 33 subjects (33%), grade 3 neutropenia in 6 (18%), and infusion related reactions (IRR) in 14 (42%), with 1 grade 3 IRR. Any grade neuropathy occurred in 7 subjects (21%), with grade 3 neuropathy in 1 (3%). The most frequent adverse events are shown in **Table 18**.

Table 18. Adverse event observed in at least two prostate cancer subjects treated with FOR46.

Adverse Event	Number of Patients n (%) n = 35		
	Worst Grade by Patient		
	Any Grade	3	4
Infusion related reaction	14 (40)	1 (3)	-
Neutropenia	12 (34)	3 (9)	5 (14)
Neutrophil count decreased	10 (29)	3 (9)	6 (17)
White blood cell count decreased	8 (23)	3 (9)	1 (3)
Fatigue	7 (20)	1 (3)	-
Neuropathy peripheral	7 (20)	1 (3)	-
Diarrhea	6 (17)	1 (3)	-
Anemia	5 (14)	1 (3)	-
Lymphocyte count decreased	5 (14)	1 (3)	1 (3)
Nausea	5 (14)	-	-
Alopecia	5 (14)	-	-
Hypokalemia	4 (11)	-	-
ALT increased	3 (9)	-	-
Constipation	3 (9)	-	-
Decreased appetite	3 (9)	-	-
Hypomagnesaemia	3 (9)	-	-
Leukopenia	2 (6)	-	1 (3)
Lymphopenia	2 (6)	-	-
AST increased	2 (6)	-	-
Hepatic enzyme increased	2 (6)	-	-
Chills	2 (6)	-	-
Pyrexia	2 (6)	-	-
Headache	2 (6)	-	-
Hyponatremia	2 (6)	1 (3)	-

Hypophosphatemia	2 (6)	-	-
Dyspnea	2 (6)	-	-

[00177] A dose expansion study has been initiated for subjects with prostate adenocarcinoma. CD46 expression is determined at enrollment by immunofluorescence microscopy. Three patients with moderate or strongly positive CD46 expression have been enrolled. A fourth subject negative for CD46 expression was not enrolled.

[00178] This example demonstrates that FOR46 has an acceptable toxicity profile using adjusted body weight dosing, and provides encouraging preliminary evidence of efficacy in androgen signaling inhibitor-resistant mCRPC subjects. FOR46 is currently being evaluated in two mCRPC expansion cohorts: adenocarcinoma and t-SCNC.

Example 5: Dose Escalation Study - treatment of relapsed or refractory multiple myeloma with FOR46

[00179] A dose escalation clinical trial is in progress to treat human subjects having relapsed or refractory multiple myeloma with the FOR46 drug product described in Example 2. To be eligible a patient's prior therapy must have included a proteasome inhibitor, an immunomodulatory imide drug (ImiD) and a CD38-directed therapy. Eligible patients also have the following organ function indicators: Hemoglobin $\geq$ 8 g/dL, ANC $\geq$ 1500/µL; Platelets $\geq$ 100k; ALT/AST $\leq$ 2.5 x upper limit of normal (ULN); Bilirubin $\leq$ 1.5 mg/dL; and Creatinine $\leq$ 1.5 x ULN. FOR46 was administered once every three weeks with infusion-related reaction prophylaxis by IV infusion over 30-60 minutes.

[00180] The initial protocol had 2.4 mg/kg actual weight as the highest dose. When the MTD was not defined using adjusted body weight dosing, escalation was held pending protocol amendment to allow a higher dose.

[00181] A dose expansion clinical trial with 10 patients dosed with FOR46 at 2.4 mg/kg adjusted body weight is also in progress. The eligibility criteria for the dose expansion trial were the same as for the dose escalation trial except ANC $\geq$ 1000/µL and Platelets $\geq$ 75k.

[00182] For the dose escalation trial, fifteen subjects were enrolled at 6 pre-defined dose levels from 0.1 to 2.4 mg/kg with 1 patient each at the 0.1, 0.3 and 0.6 mg/kg dose levels, 3 at 1.2 and 1.8 mg/kg and 6 at 2.4 mg/kg. The median age was 68 (range 33 – 79) with 4 females. Gain 1q was present in 9 pts, absent in 5 pts and unknown in 1. The median number of prior lines of therapy was 6 (range 3-17). Dosing for the dose escalation and dose expansion trials is shown in **Table 19**. Patient characteristics are shown in **Tables 20 and 21**.

Table 19. Dosing for the dose escalation and dose expansion trials of FOR46 for relapsing or refractory multiple myeloma

Dose Level (mg/kg q 3 weeks)	N (25)
0.1	1
0.3	1
0.6	1
1.2	3
1.8	3
2.4 (Escalation – Actual / AJBW Dosing)	6 (3 / 3)
2.4 (Expansion – AJBW)	10

Table 20. Demographics of subjects in dose escalation and dose expansion trials of FOR46 for relapsing or refractory multiple myeloma

Characteristic	Escalation (n = 15) and Expansion (n = 10)
Median age (range)	67 (33-79)
Gender F / M	7/ 18
Race – White / Black / Hispanic / Unknown	19 / 2 / 1 / 2
Myeloma Light Chain	
Kappa LC	18 (2 light chain only)
Lambda LC	6
Immunoglobulin	
IgA	6
IgG	15
IgM	1

Table 21. Prior therapies for subjects in dose escalation and dose expansion trials of FOR46 for relapsing or refractory multiple myeloma

Prior Therapies, n (%)	Escalation (n=15) and Expansion (n =10)
Median (range)	8 (3-19)
Received ≥ 5 lines of therapy	21 (84)
Proteasome Inhibitor, received/refractory	25 (100) / 21 (84)
IMiD, received/refractory	25 (100) / 22 (88)
Pomalidomide, received/refractory	20 (80) / 18 (72)
Anti-CD38 therapy, received/refractory	25 (100) / 23 (92)
Carfilzomib, received/refractory	23 (92) / 23 (92)

[00183] An accelerated titration followed by 3+3 dose escalation design is underway in the dose escalation trial. FOR46, at protocol specified doses, was infused intravenously over 30-60 minutes on Day 1 of 21-day cycles. Following excess toxicity (neutropenia and fatigue) in a subject with a high body mass index (BMI), dosing was changed from actual weight (AW) to adjusted body weight (AJBW). G-CSF secondary prophylaxis was administered to subjects experiencing grade ≥ 3 neutropenia during a previous treatment cycle.

[00184] Safety was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Dexamethasone was only allowed for infusion reaction prophylaxis. CD46 antigen density was determined on patient MM cells via flow cytometry. Treatment efficacy was monitored by measuring immunoglobulin levels (M-proteins) in serum or urine, including IgA, lambda light chain (λ), kappa light chain (κ), and M-spike proteins.

[00185] The only dose-limiting toxicity was grade 4 neutropenia in 1 high BMI patient dosed by AW. This was the only dose-limiting toxicity among 6 pts at 2.4 mg/kg dosed by a mix of AW (n=3) and ABW (n=3). One of 3 at 2.4 mg/kg AJBW had non-dose limiting grade 4 neutropenia. The most common related adverse event was grade 4 neutropenia in 3 patients (20%). One patient (6.7%) had grade 4 thrombocytopenia and 1 each (6.7%) had grade 3 AST elevation, neutropenia, anemia, nausea, and peripheral neuropathy (PN). Adverse events are shown in **Table 22**.

Table 22. Adverse Events in for subjects in dose escalation and dose expansion trials of FOR46 for relapsing or refractory multiple myeloma

Adverse Reaction	Number of Patients n (%) n = 25		
	Any Grade	Grade 3	Grade 4
Neutropenia	6 (24)	2 (8%)	1 (4%)
Anemia	5 (20)	4 (16%)	-
AST increased	4 (16)	2 (8%)	-
Neutrophil count decreased	4 (16)	2 (8%)	2 (8%)
Platelet count decreased	3 (12)	1 (4%)	1 (4%)
Weight decreased	3 (12)	-	-
Constipation	3 (12)	-	-
Nausea	3 (12)	1 (4%)	-
Fatigue	3 (12)	-	-
White blood cell count decreased	2 (8)	2 (8%)	-
Diarrhea	2 (8)	-	-
Vomiting	2 (8)	-	-

Pyrexia	2 (8)	-	-
Arthralgia	2 (8)	-	-
Headache	2 (8)	-	-
Peripheral neuropathy	2 (8)	-	-
Alopecia	2 (8)	-	-

[00186] In a preliminary evaluation, all patients administered FOR46 at a dose of less than 1.8 mg/kg (i.e. 0.1 mg/kg, 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg) had treatment ended due to disease progression. Treatment had been initiated for patients in the 1.8 mg/kg group. Patient 8 demonstrated a response to FOR46 treatment with a reduction in serum IgG, serum κ light chain, serum λ light chain, and urinary M-spike protein. This response provided preliminary evidence of anti-tumor activity at 1.8 mg/kg dose.

[00187] Four patients responded to FOR46 with a partial remission (PR) per IMWG criteria. BGM Durie et al. International uniform response criteria for multiple myeloma. Leukemia (2006) 1-7. See **Table 23**.

Table 23. Multiple myeloma patients responding to FOR46

Patient ID / **Myeloma Type Dose Level**	**1q gain**	**C1D1/ # Cycles**	**Ig**	**Serum FLC (mg/dL)**	**Serum M-spike (g/dL)**	**Urine M-spike (g/24 hrs)**	**Best IMWG Response**
006-05-008	Neg	2/5/20	4002	573	2.84	20.35	**PR**
IgG Kappa 1.8 mg/kg		7 cycles	1193	12.4	0.44	IFE+; no M-spike	
001-06-012	Pos	6/29/20	1440	21.2	1.4	-	**PR**
IgA Kappa 2.4 mg/kg ABW		12	353	10.7	0.3	-	
003-06-014	Pos	10/21/20	187 (wnl)	68.1	det	540	**PR**
IgA Kappa		9	168	34.8	det	95	
001-06-102	Pos	2/3/21	3520	131.6	2.5	-	**PR**
IgG Lambda		7	2300	56.7	1.1	-	

[00188] Of the 6 response-evaluable patients in the 1.8 and 2.4 mg/kg dose escalation cohorts, 3 had partial responses (PRs) lasting 21, 30, and 15 weeks, respectively. Of the PRs, one patient did not have gain of 1q21. In dose expansion, 3 of 10 patients were not evaluable. Of the seven evaluable patients, one had a PR lasting 18 weeks and was discontinued while in partial response

due to an adverse event of peripheral neuropathy. Two patients have ongoing stable disease through 3 and 6 cycles. Four patients had a best response of progressive disease.

[00189] Patient 006-05-008 was treated with 1.8 mg/kg FOR46. This patient is a 62-year-old white male, diagnosed with IgG Kappa MM in July 2009. The patient is 1q gain negative and was previously treated with (1) daratumumab, pomalidomide, and dexamethasone; (2) pomalidomide and dexamethasone; (3) lenalidomide; (4) lenalidomide and bortezomib; and (5) Carfilzomib and pomalidomide. IgG, κ light chain, and Serum M-spike results are shown in **FIG. 7A**.

[00190] Patient 001-06-012 was treated with 2.4 mg/kg FOR46. This patient is a 70-year-old white male who diagnosed with IgA Kappa MM in January 2013; The patient is 1q gain positive and was previously treated with (1) cyclophosphamide, bortezomib, and dexamethasone; (2) lenalidomide, bortezomib, and dexamethasone; (3) carfilzomib, cyclophosphamide, and dexamethasone; and (4) daratumumab, pomalidomide, and dexamethasone. IgA, κ light chain, and Serum M-spike results are shown in **FIG. 7B**.

[00191] Patient 003-06-014 was treated with 2.4 mg/kg (AJBW) FOR46. This patient is a 56-year-old male who was diagnosed with IgA Kappa myeloma in December 2015. The patient is 1q21 gain positive and was previously treated with (1) cyclophosphamide, bortezomib, and dexamethasone; (2) carfilzomib, lenalidomide, dexamethasone, melphalan, and ASCT, with ixazomib maintenance; (3) carfilzomib, daratumumab, and dexamethasone; and (4) CAR-T clinical trial. IgA, κ light chain, and Urine M-spike results are shown in **FIG. 7C**.

[00192] Results for all patients in the dose escalation trial are presented in **Table 24**. Results for all patients in the dose expansion trial are presented in **Table 25**. The results from both trials are summarized in **FIG. 8**.

[00193] In summary, FOR46 demonstrates an acceptable toxicity profile using adjustable body weight dosing. There is encouraging evidence of efficacy in triple refractory multiple myeloma. The dose escalation trial is being extended to 2.7 mg/kg by adjusted body weight.

Table 24. Biomarker results for refractory multiple myeloma patients treated with FOR46 in the dose escalation trial. Dose in mg/kg; C: course; D: day; EOT: end of treatment; **K:** kappa light chain; **λ:** lambda light chain. M-spike levels were measured in serum unless otherwise indicated.

Patient (Dose)	Analyte	Reference Range	Screen	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10	C11	C12	EOT or Status
1 (0.1)	IgA	672-1760 mg/dL		2230												EOT 3750
	K	5.7-26.3 mg/L	1718.9	1772.4												EOT 3330.2
	M-spike	Not detected	1.5	2.1												2.5
2 (0.3)	**K**	3.3 - 19.4 mg/L	179.9	201.4												EOT 648.7
	M-spike	Not detected	0													
3 (0.6)	IgG	672-1760 mg/dL	3570	3560	3710											EOT 3560
	K	3.3 - 19.4 mg/L	9.3	11.3	9.5											EOT 12.6
	M-spike	Not detected	2.8		2.7											EOT 2.8
4 (1.2)	IgG	672-1760 mg/dL	1160	1230	1250	1380	1570	1690								EOT 1980
	K	3.3 - 19.4 mg/L	107.9	137.3	185.8	203.8	293.5	318.3								EOT 452.4
	M-Spike	0 g/dL	0.9	1.0	1.2	1.2	1.4	1.5								
5 (1.2)	IgG	700-1600 mg/dL	1551	1539	1762	-	-	-								EOT 2012
	λ	5.7 - 26.3 mg/L	281.8	331.7	415.1	-	-	-								427.7
	M-Spike	0 g/dL	1.11	1.07	1.25	-	-	-								EOT 1.43

6 (1.2)	**K**	3.3 – 19.4 mg/L	3780.3	7915.0	3874.6 C2D8	8919.2										EOT 14833.4
	M-spike	0 gm/dL	0.24	0.45	0.47	0.69										EOT 0.86
	M-spike (urine)	0 gm/dL	268.1													
7 (1.8) 1q21 pos	IgG	635-1741 mg/dL	2910	2990	3288	3596										
	K	0.33-19.4 mg/dL	258.00	290.0	398.0	EOT 1183										EOT 1183
	M-Spike	Not detected g/dL	2.30	2.27	2.35											
8 (1.8) 1q21 neg	IgG	610-1616 mg/dL	3049	4002	1899	1233	1193	1231	1373	1573	1594	1681				
	K	0.33-19.4 mg/dL	296.2	573.0	14.1	16.3	12.4	12.9	14.2	21.1	36.6	79.2				
	M-Spike	Not detected g/dL	1.86	2.84	0.87	0.44	0.50	0.56	0.60	0.72	1.01	0.96				
	M-Spike (urine, 24 hour)	Not detected g/dL	1.1			IFE+; No M-spike										
	IMWG Response						PR			PR		PD EOT				
9 (1.8) 1q21 neg	IgA	66-433 mg/dL	945	1309	1328	1285	1450	1436	1566	1510	1556					
	K	0.33-1.94 mg/dL	3.33	3.93	4.66	5.11	5.17	5.62	6.50	7.67	8.65					
	M-spike	0 g/dL	Det		Det	Det	Det	Det	Det	Det	Det					
	M-Spike (urine, 24 hour)						N/D	Det	Det	N/D						
	IMWG Response						SD			SD						
10 (2.4)	**K**		1037.5	1074	1485											
	M-spike	0 g/dL		0.06	0											

1q21 neg	IMWG Response																	
11 (2.4) **1q21 pos**	IgG	610-1616 mg/dL	1466	1585														
	K	0.33-19.4 mg/dL	20.3	26.5														
	M-Spike	0 g/dL	0.63	0.68														
	M-Spike (urine, 24 hour)	0 g/dL	114.7															
	IMWG Response																	
12 (2.4) **1q21 pos**	IgA		1510	1440	1120	948	799	653	698	634	492	417	394	353	391			
	K	3.3 - 19.4 mg/L	18.3	21.2	18.1	18.0	16.3	14.6	12.3	12.2	10.7	12.5	10.9	13.6	12.6			
	Serum M-spike	0 g/dL		1.4	1.0	0.8	0.6	0.5	0.5	0.4	0.4	0.3	0.3	0.3	0.3			
	IMWG Response						PR			PR			PR		OFF			
13 (2.4) **1q21 pos**	IgG	672-1760 mg/dL		2010														
	K	3.3 - 19.4 mg/L	135.2	139.0														
	Serum M-Spike	0 g/dL		2.5														
	IMWG Response																	
14 (2.4) **1q21 pos**	IgG	635-1741 mg/dL		345	339													
	K	.33-1.94 mg/L	28.72	68.11	48.16	42.16	36.18	34.78	35.57									
	M-Spike (urine, 24 hour)	0 mg/day	540			144	202		95									
	IMWG Response					PR	MR		PR									
15 (2.4)	IgG	635-1741 mg/dL		345	339													

1q21 neg	K	.33 – 1.94 mg/L	2.61	3.67	5.39											
	Serum M-Spike	0 g/dL		det	Not done											
	IMWG Response				NE											

Table 25. Biomarker results for refractory multiple myeloma patients treated with FOR46 in the 2.4 mg/kg (adjusted body weight) dose expansion trial. C: course; D: day; EOT: end of treatment; **K: kappa light chain; λ: lambda light chain**; PR: partial response; PD: progressive disease; D/C: discontinued care. M-spike levels were measured in serum unless otherwise indicated.

Patient ID	**Test Name**	**Reference Range**	**Screen**	**C1D1**	**C1D15**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**
005-06-101 1q gain pos	IgG	610 – 1616 mg/dL	3079	3361		3301	4029			
	Serum Lambda light chain	5.7 – 26.3 mg/dL	129	142.7		191.9	303.6			
	Serum M-spike	0 g/dL	2.14	2.22		2.6	3.21			
	IMWG Response						PD			
001-06-102 1q gain pos (87%)	IgG	672-1760 mg/dL	3440	3520		2300	1770	1310	1220	1530
	Serum Lambda light chain	5.7-26.3 mg/dL	131.6	156		56.7	31.6	59.4	97.7	128
	Serum M-spike	0 g/dL	2.4	2.5		1.6	1.5	1.1	1.0	pending
	IMWG Response							PR		

Patient ID	Test Name	Reference Range	Screen	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C6D1
006-06-103 1q gain pos	IgG	610-1616 mg/dL	8132	8441		8949	8949	D/C		
	Serum Lambda light chain	5.7-26.3 mg/L	384.1	328.1		477.4	442.2			
	Serum M-spike	0 g/dL	6.35	6.53		7.98	7.54	PD		
	IMWG Response									
005-06-104 1q gain?	IgG	672 – 1760 mg/dL	1872	1706		1357				
	Serum Lambda light chain	3.3 – 19.4 mg/dL	1790	838		1113				
	Serum M-spike	0 g/dL	1.33	1.37		1.31				
	IMWG Response									
001-06-105 1q gain neg	IgG	672-1760 mg/dL	7350	7800		7150				
	Serum Lambda light chain	3.3 – 19.4 mg/dL	141	106.7		131.9				
	Serum M-spike	0 g/dL	4.7	5.0		5.0				
	IMWG Response									
006-06-106 1q gain pos	IgG	35 – 242 mg/dL	3548	2820		2687	2992			

Patient ID	Test Name	Reference Range	Screen	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C6D1
88% of cells 3 copies	Serum Lambda light chain	5.7 – 26.3 mg/dL	49.4	46.5		77.7	82.0			
	Serum M-spike (M1+M2)	0 g/dL	1.79	1.43		1.42	1.44			
	IMWG Response									
001-06-107 1q gain pos	IgG	672 – 1760 mg/dL	3870	3900		3940	4990 EOT			
	Serum Lambda light chain	3.3 – 19.4 mg/dL	121.2	106.6		174.1	272.7			
	Serum M-spike	0 g/dL	3.2	3.5		3.6				
	IMWG Response									
001-06-108 1q gain pos	IgG	672 – 1760 mg/dL	5250	5550	5430	5630	5280 EOT			
	Serum Lambda light chain	3.3 – 19.4 mg/dL	963.8	1022.5	643.1	1162	1247			
	Serum M-spike	0 g/dL	3.9	3.9	3.7	3.6	3.4			
	IMWG Response									
001-06-109 1q gain pos	IgG	672-1760 mg/dL	3430	5050						
	Serum Lambda light chain	3.3 – 19.4 mg/dL	15.9							

Patient ID	Test Name	Reference Range	Screen	C1D1	C1D15	C2D1	C3D1	C4D1	C5D1	C6D1
	Serum M-spike	0 g/dL	2.9							
	LDH	125-243 U/L	710							
	IMWG Response									
002-06-110 1q gain pos	IgG	35 – 242 mg/dL	660	611						
	Serum Lambda light chain	5.7 – 26.3 mg/dL	2.09							
	Serum M-spike (M1+M2)	0 g/dL								
	IMWG Response									

Example 6: Formulation of FOR46

[00194] The objective of this study was to develop an optimized formulation for FOR46. The thermal stability study, freeze-thaw stability study and agitation study were performed in the formulation development process. Stability of the drug product was evaluated by assays including the general appearance, protein concentration, pH as well as SEC-HPLC, cIEF, Caliper-SDS_R/NR and MFI analysis in order to select the optimal formulation.

ANALYTICAL METHODS

Appearance

[00195] The appearance of all samples, including clarity, color and visible particles, was examined against black and white background using a YB-2 light box.

pH

[00196] Sample pH was measured using a Seven Multi S4.0 pH meter with an Inlab®Micro electrode. The pH meter was calibrated prior to use each time.

Protein Concentration

[00197] Protein concentration was determined by UV280 readings using a NanoDrop 2000 spectrophotometer. The extinction coefficient used in all evaluation studies was 1.571AU*mL*mg-l*cm-1 All measurements were repeated twice with 2.5 µL sample each time and an average result was reported.

SEC-HPLC

[00198] Size exclusion chromatography was performed using an Agilent 1260 Infinity system with the TSKGel G3000SWXL size exclusion chromatography column (300 x 7.8 mm, 5 gm) at 25°C. The flow rate was set at 1.0 mL/min in isocratic gradient. The mobile phase was consisted of 50 mM sodium phosphate buffer, 300 mM NaCl with pH 6.8 ±0.1 for each sample. A loading amount of 100µg sample was injected and detected at 280 nm with a UV detector. Data was analyzed using Waters Empower.

cIEF

[00199] The cIEF was performed on ProteinSimple iCE3 equipment with FC-coated cIEF cartridge. In the formulation development stage, 50 µg of each sample was mixed with 100 11 L of master mix which was consisted of pI marker 4.22/7.46, Servalyt 2-9, Servalyt 3-5, 1% methyl cellulose solution and 8M urea solution. After mixing, the sample was focused for 1 minute at

1500 V and for 8 minutes at 3000 V. Detection wavelength was set 280 nm to evaluate the charge variants distribution in different pI range. In the forced degradation study, the pI marker in the master mix was changed to 4.22/7.05.

Caliper-SDS_R&NR

[00200] Before sample was tested, pretreatments such as incubation with sample buffer, SDS and N-ethylmaleimide (for non-reduced or NR) or dithiothreitol (for reduced or R) at 70°C for 10 min were necessary. Then the loading mix with a minimum volume of 42 µL (final protein concentration of 0.045 mg/mL) was test by LabChip GXII Touch at excitation/emission wavelength of 635 and 700 nm. The final results were analyzed by the commercial software: LabChip GX Reviewer.

CE-SDS_R/NR

[00201] Non-reduced CE-SDS was performed using a Beckman Coulter PA800 Enhanced or PA800 Plus instrument equipped with a photodiode array detector. Samples were diluted to 4 mg/mL by Dilution Solution (PB-CA), and then heated in the presence of 75 µl SDS sample buffer and 5µl 100 mM NEM at 60°C for 10 min for non-reduced CE-SDS. Samples were injected using +5 kV for 15 s followed by separation at +11 kV for 30 min. Detection was performed at 220 nm.

DSC analysis

[00202] The DSC analysis was performed by MicroCalTM VP-Capillary DSC System from GE Healthcare, model AS12-001C. The protein sample was first diluted to 1 mg/mL with formulation buffer before analysis. 300 µL of tested protein sample was added to 96-well plate and 300 µL of its corresponding buffer was added as reference. The samples were heated from 10°C to 110°C at a heating rate of 200 °C /h in the capillary DSC system. The sample was tested twice and the DSC results (Tm Onset and Tm values) were analyzed by Origin 7.0 DSC Automated Analysis software.

3. Excipient screening

3.1 Study Objective

[00203] This study was to evaluate the influence of NaCl, Arg-HC1, sucrose and trehalose on stabilizing FOR46 in the selected buffer.

3.2 Study Parameters

[00204] FOR46 was formulated at a concentration of 10 mg/mL in 20mM Histidine buffers pH 6.0. As given in Table 1,for each formulation, 140mM NaCl, 150 mM Arg-HC1, 8% (w/v) sucrose or trehalose was added as stabilizer, respectively, and no adding was set as blank.

[00205] The sample in each formulation was subjected to up to five cycles of freeze/thaw stress and thermal stress (40°C and 25°C). The stability of the FOR46 in each formulation was evaluated with different assays as given in **Table 26**.

Table 26. Formulation options.

F#	Buffer	pH	Excipients
F1	20mM Histidine	6.0	140 mM NaCl
F2	20mM Histidine	6.0	150 mM Arg-HCl
F3	20mM Histidine	6.0	8% Sucrose
F4	20mM Histidine	6.0	8% Trehalose
F5	20mM Histidine	6.0	/

Table 27. Stability study plan for excipient screening.

F #	Stress	Condition	T 0	Sampling points and Assay		
F1, F2, F3, F4 and F5	**Thermal**	25℃	**x**		2W	4W
					x	**x**
		40℃		1W	2W	4W
				x	**x**	**x**
	Freeze and Thaw	-40℃ to RT		3C	5C	
				x	**x**	

X= Appearance, pH, protein concentration, SEC-HPLC, cIEF, Caliper-SDS, DAR

3.4 Sample Preparation

[00206] FOR46 was buffer exchanged to 20mM Histidine at pH 6.0 via the ultrafiltration method. After adding appropriate amount of sucrose, trehalose, Arg-HC1 or NaCl, the protein concentration was adjusted to 10 mg/mL then all samples were aseptically filtered with 0.22-μm PES membrane filter. For each formulation sample, eight (8) 2R glass vials were filled with 1 mL of filtered DS. One (1) vial was subjected to three and five cycles of freeze and thaw stress, respectively. In each cycle, the freezing time was at least 12 hours in a -40°C freezer. The sample was thawed at room temperature. Three (3) vials were incubated at 40°C. Two vials were

incubated at 25°C. One vial from each study condition was sampled for analysis at the designated time point. One (1) vial served as TO.

3.5 Results and Discussion

3.5.1 Appearance, protein concentration and pH results

[00207] Obvious precipitation was observed in Fl and F2 right after a short storage at 5°C , which could be attributed to the high ionic strength in formulations. Therefore, Fl and F2 were excluded from the study. All the rest of the samples were colorless, slightly opalescent and free of visible particles at the beginning of the study.

[00208] After incubation at 25°C as well as 40s for up to 4 weeks, F5 were free of visible particles and many particles were observed in both F3 and F4. It could be attributed to protein denaturation induced by higher surface tension of formulations with sugar, and the referring adverse effect could be eliminated by addition of surfactant in finalized formulation.

[00209] No substantial change in appearance was found in F3, F4 and F5 after up to 5 cycles of freeze and thaw stress.

[00210] No substantial change in pH and protein concentration was found at 40°C, 25°C and after 5 cycles of freeze and thaw.

SEC purity

[00211] The SEC purity data was summarized in **Table 28**. Based on SEC data at 25°C and after up to 5 cycles of Freeze and Thaw, no substantial change was found in any samples. After incubation for 4 weeks at 40°C , the SEC purity of F5 was obviously lower than F3 and F4. So, it could be concluded that the stabilizing effect of sucrose and trehalose to ADC was unexpectedly substantial and comparable.

Table 28. SEC purity results of FOR46 excipient screening study.

Sample information		T0	FT		25°C		40°C		
			3C	5C	2W	4W	1W	2W	4W
F3	Main peak%	97.9	98.6	98.5	97.5	98.1	96.0	93.2	94.9
	HMW%	2.0	1.3	1.3	2.3	1.6	3.8	4.6	4.22
	LMW%	0.1	0.2	0.2	0.1	0.3	0.2	2.1	0.92
F4	Main peak%	97.9	98.6	98.5	97.5	98.1	95.9	93.2	94.6
	HMW%	2.0	1.2	1.3	2.3	1.6	3.9	4.8	4.4
	LMW%	0.1	0.2	0.2	0.2	0.3	0.3	2.0	0.9
F5	Main peak%	97.5	98.4	98.4	96.8	97.8	94.7	90.8	92.6
	HMW%	2.4	1.4	1.4	3.0	1.9	4.9	6.3	6.2
	LMW%	0.1	0.2	0.2	0.2	0.4	0.4	2.9	1.2

Caliper-SDS_R/NR purity

[00212] No substantial change in Caliper-SDS_R/NR purity was found in any samples after up to 5 cycles of Freeze and Thaw and incubation for 4 weeks at 25°C as well as 40°C.

cIEF

[00213] Based on cIEF data, a substantial decrease in main peak purity was found in all samples after incubation for 4 weeks at 40°C as well as 25°C, and the decrease speed was comparable among F3-F5. No substantial change was found after up to 5 cycles of Freeze and Thaw.

Drug to antibody ratio (DAR)

[00214] No substantial change in DAR was found in all samples after incubation for 4 weeks at 40°C as well as 25°C and up to 5 cycles of freeze and thaw.

Conclusion

[00215] Even though the worse appearance was observed in buffer with trehalose and sucrose, the adverse effect induced by higher surface tension would be reversible by addition of surfactant. Surprisingly, the SEC purity results indicated that sucrose and trehalose showed the outstanding and comparable performance in stabilizing FOR46 against thermal stress. Considering the commercial cost, the sucrose was selected as excipient in optimized formulation. The surfactant screening study will be performed in 20 mM Histidne buffer at pH 6.0 with 8% (w/v) sucrose (F3).

4. Surfactant screening

[00216] This study was to evaluate the stabilizing effect of 2 different surfactants (PS-80 and PS-20) at 3 content levels in 20 mM Histidine buffer with 8% (w/v) sucrose. Based on DAR data (given in Table 34), no substantial change in DAR was found in all samples after incubation for 4 weeks at 40°C as well as 25°C and up to 5 cycles of freeze and thaw.

Study Parameters

[00217] FOR46 was formulated at 10 mg/mL in 20mM Histidine buffer at pH 6.0 with 8% (w/v) sucrose in 7 formulations as given in **Table 29**. PS-80 or PS-20 with 3 content levels respectively was added to each formulation and the formulation without surfactant was included as blank. The sample in each formulation was subjected to up to five cycles of freeze and thaw, thermal stress (40°C) and agitation stress (300rpm, 2 days). The stability of the ADC at designated time point was evaluated with different assays.

Table 29. Formulation option of FOR46 excipient screening.

Formulation No.	pH/buffer	Excipients	Surfactant Comments
1	20 mM His, pH6.0	8% sucrose	NA
2			0.01% PS-80
3			0.02% PS-80
4			0.03% PS-80
5			0.015% PS-20
6			0.02% PS-20
7			0.03% PS-20

Table 30. Formulation option of FOR46 excipient screening.

Attributes	Condition	T0	Sampling Points and Assay	
Thermal	40° C	X,Y, Z	2W	4W
			X	X, Z
Freeze/Thaw	-40°C to RT		5 Cycles	
			X,Y, Z	
Agitation	25°C,300 rpm		2D	
			X,Y, Z	

X=Appearance, pH, protein concentration SEC-HPLC, cIEF, SDS caliper_R; Y=MFI; Z=binding antigen

4.3 Drug Materials

[00218] FOR46 formulated in 20 mM histidine buffer at pH 6.0 with 8% (w/v) sucrose was stored at 2-8 °C before the surfactant screening study.

Sample Preparation

[00219] After adding the designed amount of PS-80 or PS-20, WBP2O95 ADC DS was aseptically filtered with 0.22-μm PES membrane filter. For each formulation sample, eight (8) 2R glass vials were filled with 1 mL of filtered DS, respectively. Two (2) vials was subjected to five cycles of freeze and thaw stress. In each cycle, the freezing time was at least 12 hours in a -40°C freezer. The sample was thawed at room temperature. Two (2) vials were incubated at 40°C. Two (2) vials were subjected to agitation for 2 days at a speed of 300 rpm at ambient temperature. One vial from 40°C and two vials from Freeze and Thaw stress as well as agitation stress was sampled for analysis at the designated time point. Two (2) vial served as TO.

4.5 Results and Discussion

4.5.1 Appearance, protein concentration and pH results

[00220] After 5 cycles of freeze and thaw, no substantial change in appearance was found among all samples. After agitation for 2 days at a speed of 3OOrpm and incubation for 4 weeks at 40°C, particles and fibers were observed in F1 (without surfactant). It indicated that the presence of surfactant could be essential to protect ADC in thermal and agitation stress condition.

[00221] No substantial change was found in pH and protein concentration.

4.5.2 SEC purity

[00222] After 5 cycles of freeze and thaw and agitation for 2 days, no substantial change in SEC purity was found. After incubation at 40°C for 4 weeks, a decline of 6% in main peak purity was found in all 7 formulations. Based on SEC purity data, all formulations were comparable in all conditions.

4.5.3 CE-SDS_R purity

[00223] No substantial change in CE-SDS R purity was found in thermal stress, freeze and thaw and agitation stress condition.

4.5.4 cIEF

[00224] After 5 cycles of freeze and thaw and agitation for 2 days, no substantial change in cIEF was found. In thermal stress, the main peak purity decreased substantially while the acid peak purity increased accordingly. However, the change among all formulations was comparable.

4.5.5 Potency

[00225] Based on previous data, 3 leading formulations (F2, F3 and F4) were selected to perform binding potency assay. In thermal stress, agitation stress and freeze and thaw stress, no substantial change in binding potency was found.

4.5.6 MFI

[00226] Surprisingly, based on MFI results, more than 10 times of particles in Fl was found compared to the rest formulations. It suggested more sub-visible particles in F1 than the other formulations.

Table 31. MFI results of FOR46 in surfactant screening study.

Sample		T0	FT	Agitation
F1	2~5um	7085	2561	4874
	5~10um	1340	523	1337
	10~25um	194	79	478
	⩾25um	15	4	69
F2	2~5um	542	368	404
	5~10um	104	51	33
	10~25um	22	9	5
	⩾25um	0	0	0
F3	2~5um	1467	340	258
	5~10um	379	35	15
	10~25um	94	10	4
	⩾25um	2	0	0
F4	2~5um	545	969	332
	5~10um	53	109	56
	10~25um	7	12	10
	⩾25um	4	0	2
F5	2~5um	692	716	1050
	5~10um	84	60	99
	10~25um	10	9	4
	⩾25um	0	0	0
F6	2~5um	550	337	294
	5~10um	63	30	25
	10~25um	20	12	10
	⩾25um	5	2	4

F7	2~5um	813	965	689
	5~10um	114	171	130
	10~25um	30	33	78
	⩾25um	30	33	78

4.6 Conclusion

[00227] Based on appearance and MFI results, surfactant played an unexpectedly important role in protecting ADC in thermal and agitation stress condition. However, no difference was found among 6 formulations with two different surfactants (PS-80 and PS-20) at three content levels. Considering the lower CMC (critical micelle concentration) of PS-80 compared to PS-20, which suggested the lower effective concentration of surfactant, and the probable adverse effect introduced by degradation of PS-80 at high content level, 0.01% (w/v) PS-80 was selected in the final formulation.

[00228] FOR46 (10mg/mL) in 20 mM histidine buffer at pH 6.0 with 8% (w/v) sucrose and 0.01% (w/v) PS-80 was selected as the final formulation.

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 chain; and

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

101. 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;

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

102. The immunoconjugate of claim 101, wherein said cancer is relapsed or refractory multiple myeloma (RRMM).

103. The immunoconjugate of claim 101, 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.

105. The immunoconjugate of any one of claim 101 - 104, wherein said cell comprises CD46 as determined by immunofluorescence microscopy or immunohistochemistry.

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

107. The immunoconjugate of any one of claim 101 - 104, wherein said cell comprises an amplification of chromosome location 1q21.

108. The immunoconjugate of any one of claim 101 - 107, wherein said immunoconjugate is formulated for intravenous infusion.

109. The immunoconjugate of any one of claim 101 - 108, 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.

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

111. The immunoconjugate of any one of claims 101 - 110, wherein said immunoconjugate is administered at a dose from about 1.2 to about 3.0 mg/kg.

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.

113. The immunoconjugate of any one of claims 111 - 112, wherein the weight, in kg, of said human subject is an actual body weight.

114. The immunoconjugate of any one of claims 111 - 112, wherein the weight, in kg, of said human subject is an adjusted body weight.

115. The immunoconjugate of any one of claims 111 - 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.

166. A pharmaceutical formulation for the treatment of metastatic castration resistant prostate cancer 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.

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.