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

[0002a] In one aspect, provided herein is 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 heavy chain; and

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

[0002b] In another aspect, provided herein is a pharmaceutical composition comprising the immunoconjugate as described herein 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.

[0002c] In another aspect, provided herein is use of an immunoconjugate or pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of a cancer in a human subject comprising a cell expressing CD46.

[0002d] In another aspect, provided herein is use of a pharmaceutical formulation in the manufacture of a medicament for the treatment of metastatic castration resistant prostate cancer in a human subject in need thereof, wherein the pharmaceutical formulation comprises an immunoconjugate at a concentration of about 10.0 ± 1.0 mg/mL, wherein the immunoconjugate comprises:

a recombinant antibody comprising:

a first heavy chain comprising SEQ ID NO: 9,

a first light chain comprising SEQ ID NO: 10,

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

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

one, two, three or four pairs of adducts;

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

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

wherein said pairs of cysteine residues are selected from:

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

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

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

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

about 20 mM histidine buffer at pH 6.0,

about 8.0% sucrose, and

about 0.01% polysorbate 80.

[0002e] In another aspect, provided herein is the immunoconjugate or pharmaceutical composition as described herein or the pharmaceutical formulation as described herein for use in therapy.

[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