

PHARMACEUTICAL COMPOSITIONS COMPRISING ANTI-191P4D12 ANTIBODY DRUG CONJUGATES AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application No. 62/774,819, filed December 3, 2018, the disclosure of which is incorporated by reference herein in its entirety.

1. Field

[0001] Provided herein are pharmaceutical compositions comprising anti-191P4D12 antibody drug conjugates. Methods of using the pharmaceutical compositions are also provided herein.

2. Background

[0002] Drug substances are usually administered as part of a formulation in combination with one or more other agents that serve varied and specialized pharmaceutical functions. Pharmaceutical excipients have various functions and contribute to the pharmaceutical formulations in many different ways, *e.g.*, solubilization, dilution, thickening, stabilization, preservation, coloring, flavoring, *etc.* Properties that may be considered when formulating an active drug substance include bioavailability, ease of manufacture, ease of administration, and stability of the dosage form. Due to the varying properties of active drug substances being formulated, dosage forms typically require pharmaceutical excipients that are uniquely tailored to the active drug substance in order to achieve advantageous physical and pharmaceutical properties.

[0003] Thus, a need exists as to pharmaceutical compositions of anti-191P4D12 antibody drug conjugates having advantageous physical and pharmaceutical properties. The present invention satisfies this need and provides related benefits.

3. Summary

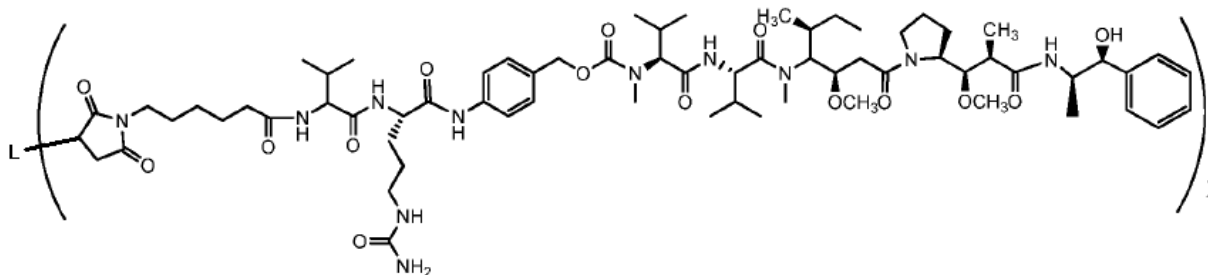
[0004] In one aspect, the present disclosure provides a pharmaceutical composition comprising (a) an antibody drug conjugate comprising an antibody or antigen binding fragment thereof that binds to 191P4D12 conjugated to one or more units of monomethyl auristatin E (MMAE), wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:7 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:8; and (b) a pharmaceutically acceptable excipient comprising L-histidine in the range of 5 and 50 mM, polysorbate-20 (TWEEN-20) in the range of from 0.001 to 0.1% (w/v), trehalose dihydrate in the range of 4% and 7% (w/v), and HCl, wherein the pH is in a range of 5.5 to 6.5 at 15°C to 27°C. In one aspect example, provided herein is a pharmaceutical composition comprising (a) an antibody drug conjugate comprising an antibody or antigen binding fragment thereof that binds to 191P4D12 conjugated to one or more units of monomethyl auristatin E (MMAE), wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region

pH is about 6.0 at 25°C.

[0035] In some examples, the antibody drug conjugate is at the concentration of about 10 mg/mL in the pharmaceutical composition provided herein.

[0036] In yet other specific examples, the pharmaceutical composition provided herein comprises:

(a) an antibody drug conjugate comprising the following structure:



wherein L- represents the antibody or antigen binding fragment thereof and p is from 1 to 10;
and

(b) a pharmaceutically acceptable excipient comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.0% (w/v) sucrose, and HCl, wherein the pH is about 6.0 at 25°C.

[0037] In some examples, the antibody drug conjugate is at the concentration of about 10 mg/mL in the pharmaceutical composition provided herein.

[0038] In some examples, the pharmaceutical composition provided herein is in a liquid form.

[0039] In other examples, the pharmaceutical composition provided herein is lyophilized.

[0040] In another aspect, provided herein is a lyophilized composition made by freeze-drying the pharmaceutical composition provided herein.

[0041] In some examples, the pharmaceutical composition is stored at -80°C, 4°C, 25°C or 37°C.

[0042] In another example, provided herein is a method of preventing or treating a disease or disorder in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition provided herein.

[0042a] In another aspect, provided herein is a pharmaceutical composition as provided herein for use in ~~preventing or treating a disease or disorder~~cancer in a subject.

What is Claimed is:

1. A pharmaceutical composition comprising

(a) an antibody drug conjugate comprising an antibody or antigen binding fragment thereof that binds to 191P4D12 conjugated to one or more units of monomethyl auristatin E (MMAE), wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:7 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:8; and

(b) a pharmaceutically acceptable excipient comprising L-histidine in the range of 5 and 50 mM, polysorbate-20 (TWEEN-20) in the range of from 0.001 to 0.1% (w/v), ~~and at least one of~~ trehalose dihydrate in the range of 4% and 7% (w/v), and HCl, wherein the pH is in a range of 5.5 to 6.5 at 15°C to 27°C ~~sucrose~~.

2. The pharmaceutical composition of claim 1, wherein

(a) the antibody or antigen binding fragment thereof comprises CDR H1 comprising an amino acid sequence of SEQ ID NO:9, CDR H2 comprising an amino acid sequence of SEQ ID NO:10, CDR H3 comprising an amino acid sequence of SEQ ID NO:11; CDR L1 comprising an amino acid sequence of SEQ ID NO:12, CDR L2 comprising an amino acid sequence of SEQ ID NO:13, and CDR L3 comprising an amino acid sequence of SEQ ID NO:14;

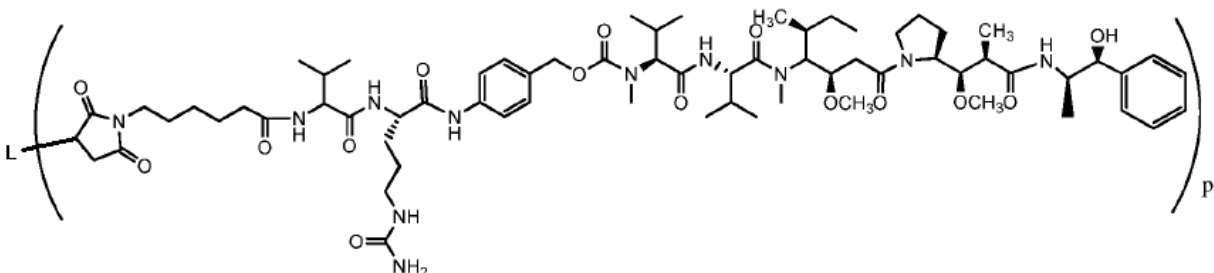
(b) the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 136th amino acid (serine) of SEQ ID NO:7 and a light chain variable region comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 130th amino acid (arginine) of SEQ ID NO:8; or

(c) the antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8.

3. The pharmaceutical composition of claim 1 or 2, wherein

- (a) the antigen binding fragment is an Fab, F(ab')₂, Fv or scFv-~~fragment~~;
- (b) the antibody is a fully human antibody; or
- (c) the antibody or antigen binding fragment thereof is a recombinant antibody or antigen binding fragment thereof~~recombinantly produced~~.

4. The pharmaceutical composition of any one of claims 1 to 3, wherein the antibody drug conjugate has the following structure:

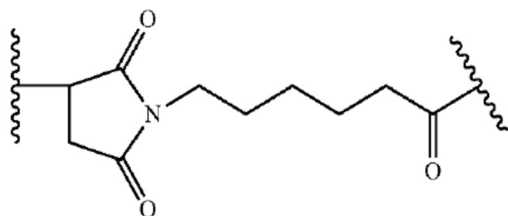


wherein L- represents the antibody or antigen binding fragment thereof and p is from 1 to 10;
wherein optionally p is from 2 to 8.

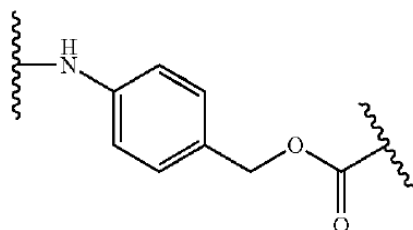
5. The pharmaceutical composition of claim 8, wherein p is 3.8.

56. The pharmaceutical composition of claim 1, wherein the antibody or antigen binding fragment thereof is linked to each unit of monomethyl auristatin E (MMAE) via a linker; wherein

- (a) optionally the linker is an enzyme-cleavable linker, and the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof; or
- (b) optionally the linker has a formula of: $-A_a-W_w-Y_y-$; wherein $-A-$ is a stretcher unit, a is 0 or 1; $-W-$ is an amino acid unit, w is an integer ranging from 0 to 12; and $-Y-$ is a spacer unit, y is 0, 1, or 2; wherein
 - (i) optionally the stretcher unit has the structure of Formula (1) below; the amino acid unit is valine citrulline; and the spacer unit is a PAB group comprising the structure of Formula (2) below:



Formula (1)



Formula (2); or

(ii) optionally the stretcher unit forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof, and the spacer unit is linked to MMAE via a carbamate group.

67. The pharmaceutical composition of any one of claims 1 to **56**, comprising the antibody drug conjugate at a concentration of (i) from 1 to 20 mg/mL; (ii) from 5 to 15 mg/mL; (iii) from 8 to 12 mg/mL; or (iv) about 10 mg/mL.

78. The pharmaceutical composition of any one of claims 1 to **67**, wherein the L-histidine is present (i) ~~in the range of 5 to 50 mM~~; (ii) in the range of 10 to 40 mM; (iii) in the range of 15 to 35 mM; (iii~~v~~) in the range of 15 to 30 mM; (iv) in the range of 15 to 25 mM; or (v~~i~~) at about 20 mM.

89. The pharmaceutical composition of any one of claims 1 to **78**, wherein the concentration of TWEEN-20 is (i) ~~in the range of from 0.001 to 0.1% (v/v)~~; (ii) in the range of from 0.0025 to 0.075% (v/v); (iii) in the range of from 0.005 to 0.05% (v/v); (iii~~v~~) in the range of from 0.01 to 0.03% (v/v); or (iv) about 0.02% (v/v).

910. The pharmaceutical composition of any one of claims 1 to **89**, wherein ~~the pharmaceutical composition comprises trehalose dihydrate; wherein optionally~~ the trehalose dihydrate is present (i) ~~in the range of 1 to 20% (w/v)~~; (ii) ~~in the range of 2 to 15% (w/v)~~; (iii) in

~~the range of 3 to 10% (w/v); (iv) in the range of 4 to 6% (w/v); or (ii) at about 5.5% (w/v); (vi) in the range of 50 mM to 300 mM; (vii) in the range of 75 mM to 250 mM; (viii) in the range of 100 mM to 200 mM; (ix) in the range of 130 mM to 150 mM; or (x) at about 146 mM.~~

10. — ~~The pharmaceutical composition of any one of claims 1 to 8, wherein the pharmaceutical composition comprises sucrose; wherein optionally the sucrose is present (i) in the range of 1 to 20% (w/v); (ii) in the range of 2 to 15% (w/v); (iii) in the range of 3 to 10% (w/v); (iv) in the range of 4 to 6% (w/v); (v) at about 5.5% (w/v); (vi) in the range of 50 mM to 300 mM; (vii) in the range of 75 mM to 250 mM; (viii) in the range of 100 mM to 200 mM; (ix) in the range of 130 mM to 150 mM; or (x) at about 146 mM.~~

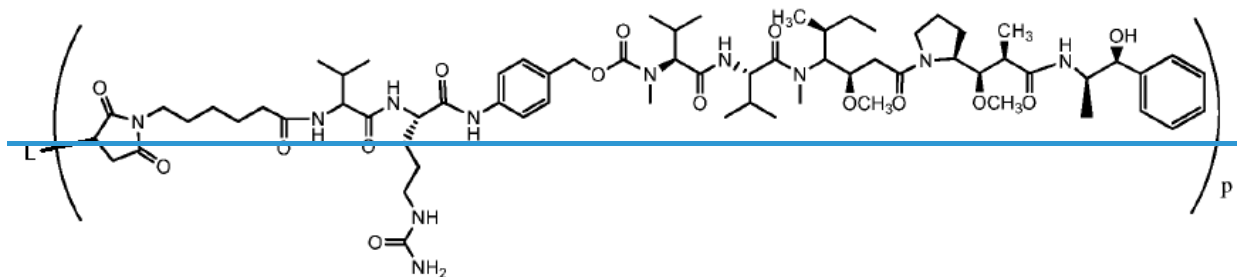
11. The pharmaceutical composition of any one of claims 1 to 10, wherein the pharmaceutical composition has a pH (i) ~~in the range of 5.5 to 6.5~~, (ii) in the range of 5.7 to 6.3, or (iii) of about 6.0; wherein optionally the pH is taken at (i) room temperature, ~~(ii) 15°C to 27°C~~, ~~(iii) 4°C~~, or (iv) 25°C.

12. The pharmaceutical composition of any one of claims 1 to 11, wherein

- ~~(a) — the pharmaceutical composition further comprises hydrochloric acid (HCl);~~
- ~~(b) — the pH is adjusted by HCl;~~
- ~~(c) — the pharmaceutical composition further comprises succinic acid; or~~
- ~~(d) — the pH is adjusted by succinic acid.~~

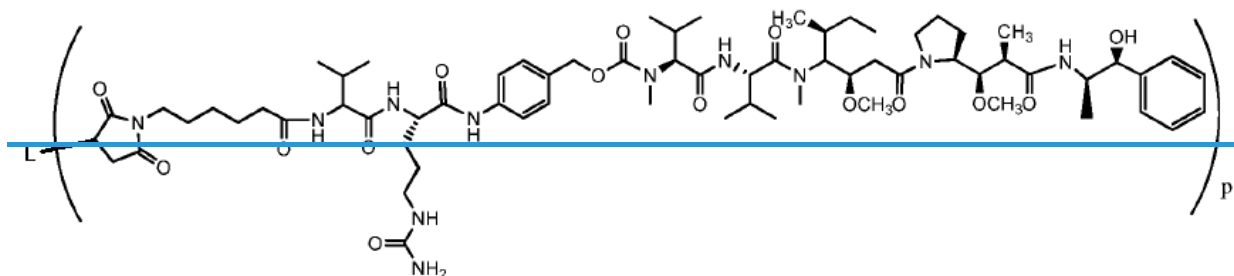
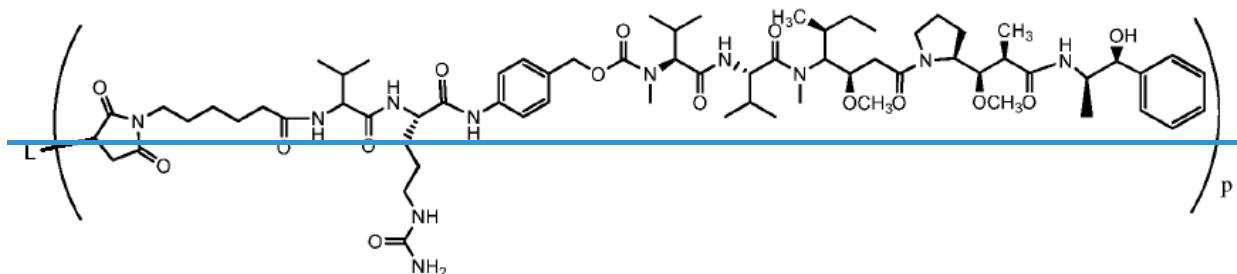
13. The pharmaceutical composition of any one of claims 1 to ~~56~~, comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, and ~~at least one of~~ about 5.5% (w/v) trehalose dihydrate ~~or about 5 % (w/v) sucrose~~; wherein

- ~~(a) — optionally the pharmaceutical composition further comprises HCl or succinic acid;~~



(b) — optionally the pH is 6.0 at room temperature or at 25°C; and

(c) — optionally the antibody drug conjugate is at a concentration of about 10 mg/mL.



14. The pharmaceutical composition of any one of claims 1 to 13, wherein

(a) the pharmaceutical composition is in a liquid form or is lyophilized; or

(b) the pharmaceutical composition is stored at -80°C, 4°C, 25°C, or 37°C.

~~15. — A lyophilized composition made by freeze-drying the pharmaceutical composition of any one of claims 1 to 13.~~

~~15.15.~~ A pharmaceutical composition as defined in any one of claims 1 to ~~15-14~~ for use in ~~preventing or treating~~ cancer ~~a disease or disorder~~ in a subject.

~~15.16.~~ Use of a pharmaceutical composition as defined in any one of claims 1 to ~~15-14~~ in the manufacture of a medicament for treating cancer in a subject; wherein

- (a) optionally the subject is a human subject;
- (b) optionally the cancer is colon cancer, pancreatic cancer, ovarian cancer, lung cancer, bladder cancer, urothelial cancer, breast cancer, esophageal cancer, head cancer, or neck cancer;
- (c) optionally the lung cancer is non-small cell lung cancer;
- (d) optionally the bladder cancer or urothelial cancer is advanced or metastatic; and
- (e) optionally the cancer has tumor cells expressing 191P4D12.

1718. The use of claim 1617, wherein the pharmaceutical composition is adapted to be ~~administrable~~ administered with a second therapeutic agent; wherein

- (a) optionally the second therapeutic agent is an immune checkpoint inhibitor;
- (b) optionally the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor;
- (c) optionally the PD-1 inhibitor is nivolumab; and
- (d) optionally the PD-L1 inhibitor is selected from a group consisting of atezolizumab, avelumab, and durvalumab.

1918. The use of claim 1716 or 1817, wherein the antibody drug conjugate formulated in the pharmaceutical composition is to be administered at a dose of (i) 1 to 10 mg/kg of the subject's body weight; (ii) 1 to 5 mg/kg of the subject's body weight; (iii) 1 to 2.5 mg/kg of the subject's body weight; (iv) 1 to 1.25 mg/kg of the subject's body weight; or (v) about 1 mg/kg or 1.25 mg/kg of the subject's body weight.

2019. The use of claim 1918, wherein the antibody drug conjugate formulated in the pharmaceutical composition is to be administered by an intravenous (IV) injection or infusion;

2120. The use of claim 2019, wherein the antibody drug conjugate formulated in the pharmaceutical composition is to be administered by an intravenous (IV) injection or infusion over about 30 minutes twice every three-week cycle; wherein

- (a) optionally the antibody drug conjugate formulated in the pharmaceutical composition is to be administered by an intravenous (IV) injection or infusion over about 30 minutes on Days 1 and 8 of every three-week cycle;

(b) optionally the pharmaceutical composition is adapted to be administrable with an immune checkpoint inhibitor by an intravenous (IV) injection or infusion on Day 1 of every three-week cycle; and

(c) optionally the immune checkpoint inhibitor is to be administered at an amount of about 100 mg to about 1500 over about 30 minutes or 60 minutes.

2221. The use of claim 2019, wherein the antibody drug conjugate formulated in the pharmaceutical composition is to be administered by an intravenous (IV) injection or infusion over about 30 minutes three times every four-week cycle; wherein

(a) optionally the antibody drug conjugate formulated in the pharmaceutical composition is to be administered by an intravenous (IV) injection or infusion over about 30 minutes on Days 1, 8 and 15 of every four-week cycle; and

(b) optionally the pharmaceutical composition is adapted to be administrable with an immune checkpoint inhibitor by an intravenous (IV) injection or infusion.