impaired antitumor immune responses (Blood 2009 114(8): 1537). This may be due to exploitation of PD-L1 signaling mediated by PD-L1 expressing tumor cells interacting with PD-1 expressing T cells to result in attenuation of T cell activation and evasion of immune surveillance (Sharpe et al., Nat Rev 2002) (Keir ME et al, 2008 Annu. Rev. Immunol. 26:677). Therefore, inhibition of the PD-L1/PD-1 interaction may enhance CD8+ T cell-mediated killing of tumors,

[0008] Therapeutic targeting PD-1 and other molecules which signal through interactions with PD-1, such as programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) are an area of intense interest. The inhibition of PD-L1 signaling has been proposed as a means to enhance T cell immunity for the treatment of cancer and infection, including both acute and chronic (e.g., persistent) infection. Formulations of anti-PD-L1 antibodies that can be used for intravenous infusion have been described (see US 2016/0319022). However, as an optimal formulation for an anti-PD-L1 antibody that is suitable for subcutaneous injection has yet to be developed, a significant unmet medical need exists.

[0009] All references cited herein, including patent applications, patent publications, and UniProtKB/Swiss-Prot Accession numbers are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

[0010] In one example, provided herein is a liquid pharmaceutical formulation, the formulation comprising a monoclonal anti-PD-L1 antibody in a concentration of about 100 g/L to about 150 g/L, histidine acetate in a concentration of about 15 mM to about 25 mM, sucrose in a concentration of about 200 mM to about 280 mM, polysorbate in a concentration of about 0.04% (w/v) to about 0.08% (w/v), methionine in a concentration of about 5 mM to about 15 mM, and pH of about 5.6 to about 6.0, wherein the monoclonal antibody comprises

(a) a light chain variable region comprising:

(1) HVR-L1 comprising the amino acid sequence RASQDVSTAVA (SEQ ID NO: 1);

(2) HVR-L2 comprising the amino acid sequence SASFLYS (SEQ ID NO:2);

(3) HVR-L3 comprising the amino acid sequence QQYLYHPAT (SEQ ID NO:3); and

(b) a heavy chain variable region comprising:

(1) HVR-H1 comprising the amino acid sequence GFTFSDSWIH (SEQ ID NO:4);

(2) HVR-H2 comprising the amino acid sequence AWISPYGGSTYYADSVKG (SEQ ID NO:5);

(3) HVR-H3 comprising the amino acid sequence WPGGFDY (SEQ ID NO:6). In some examples, the monoclonal antibody in the formulation is in a concentration of about 120 g/L to about 130 g/L. In some examples, the monoclonal antibody in the formulation is in a concentration of about 125 g/L. In some examples, the histidine acetate is in a concentration of about 17 mM to about 22 mM. In some examples, the histidine acetate is in a concentration of about 20 mM. In some examples, the sucrose is in a concentration of about 220 mM to about 260 mM. In some examples, the sucrose is in a concentration of about 240 mM. In some examples, the pH is about 5.8. In some examples, the polysorbate in the formulation is polysorbate 20. In some examples, the polysorbate is in a concentration of about 0.05% (w/v) to about 0.07% (w/v). In some examples, the polysorbate is in a concentration of about 0.06% (w/v). In some examples, the methionine is in a concentration of about 10 mM. In some examples, the formulation further comprises a hyaluronidase enzyme. In some examples, the hyaluronidase enzyme is recombinant human hyaluronidase (rHuPH20). In some examples, the hyaluronidase enzyme is in a concentration of about 1000 U/ml to about 3000 U/ml. In some examples, the hyaluronidase enzyme is in a concentration of about 2000 U/ml.

[0010a] In one aspect, the present disclosure refers to a liquid pharmaceutical formulation, the formulation comprising a monoclonal anti-PD-L1 antibody in a concentration of about 100 g/L to about 150 g/L, histidine acetate in a concentration of about 15 mM to about 25 mM, sucrose in a concentration of about 200 mM to about 280 mM, polysorbate in a concentration of about 0.04% (w/v) to about 0.08% (w/v), methionine in a concentration of about 5 mM to about 15 mM, and pH of about 5.6 to about 6.0, wherein the monoclonal antibody comprises (a) a light chain variable region comprising: (1) HVR-L1 comprising the amino acid sequence RASQDVSTAVA (SEQ ID NO: l); (2) HVR-L2 comprising the amino acid sequence SASFLYS (SEQ ID NO:2); (3) HVR-L3 comprising the amino acid sequence QQYLYHPAT (SEQ ID NO:3); and (b) a heavy chain variable region comprising: (1) HVR-H1 comprising the amino acid sequence GFTFSDSWIH (SEQ ID NO:4); (2) HVR-H2 comprising the amino acid sequence AWISPYGGSTYYADSVKG (SEQ ID NO:5); (3) HVR-H3 comprising the amino acid sequence WPGGFDY (SEQ ID NO:6).

[0011] In one example, provided herein is a liquid pharmaceutical formulation, the formulation comprising a monoclonal anti-PD-L1 antibody in a concentration of about 100 g/L to about 150 g/L, histidine acetate in a concentration of about 15 mM to about 25 mM, sucrose in a concentration of about 200 mM to about 280 mM, polysorbate in a concentration of about 0.01% (w/v) to about 0.03% (w/v), and pH of about 5.3 to about 5.7, wherein the monoclonal antibody comprises

(a) a light chain variable region comprising:

(1) HVR-L1 comprising the amino acid sequence RASQDVSTAVA (SEQ ID NO: l);

(2) HVR-L2 comprising the amino acid sequence SASFLYS (SEQ ID NO:2);

(3) HVR-L3 comprising the amino acid sequence QQYLYHPAT (SEQ ID NO:3); and

(b) a heavy chain variable region comprising:

(1) HVR-H1 comprising the amino acid sequence GFTFSDSWIH (SEQ ID NO:4);

(2) HVR-H2 comprising the amino acid sequence AWISPYGGSTYYADSVKG (SEQ ID NO:5);

(3) HVR-H3 comprising the amino acid sequence WPGGFDY (SEQ ID NO:6). In some examples, the monoclonal antibody in the formulation is in a concentration of about 120 g/L to about 130 g/L. In some examples, the monoclonal antibody in the formulation is in a concentration of about 125 g/L. In some examples, the histidine acetate is in a concentration of about 17 mM to about 22 mM. In some examples, the histidine acetate is in a concentration of about 20 mM. In some examples, the sucrose is in a concentration of about 220 mM to about 260 mM. In some examples, the sucrose is in a concentration of about 240 mM. In some examples, the pH is about 5.5. In some examples, the polysorbate in the formulation is polysorbate 20. In some examples, the polysorbate is in a concentration of about 0.02% (w/v). In some examples, the formulation is mixed with a hyaluronidase enzyme prior to being administered to a subject. In some examples, the hyaluronidase enzyme is recombinant human hyaluronidase (rHuPH20). In some examples, the hyaluronidase enzyme concentration in the mixture is about 1000 U/ml to about 3000 U/ml. In some examples, the hyaluronidase enzyme concentration in the mixture is about 2000 U/ml.

[0011a] In one aspect, the present disclosure refers to a liquid pharmaceutical formulation, the formulation comprising a monoclonal anti-PD-L1 antibody in a concentration of about 100 g/L to about 150 g/L, histidine acetate in a concentration of about 15 mM to about 25 mM, sucrose in a concentration of about 200 mM to about 280 mM, polysorbate in a concentration of about 0.01% (w/v) to about 0.03% (w/v), and pH of about 5.3 to about 5.7, wherein the monoclonal antibody comprises (a) a light chain variable region comprising: (1) HVR-L1 comprising the amino acid sequence RASQDVSTAVA (SEQ ID NO: l); (2) HVR-L2 comprising the amino acid sequence SASFLYS (SEQ ID NO:2); (3) HVR-L3 comprising the amino acid sequence QQYLYHPAT (SEQ ID NO:3); and (b) a heavy chain variable region comprising: (1) HVR-H1 comprising the amino acid sequence GFTFSDSWIH (SEQ ID NO:4); (2) HVR-H2 comprising the amino acid sequence AWISPYGGSTYYADSVKG (SEQ ID NO:5); (3) HVR-H3 comprising the amino acid sequence WPGGFDY (SEQ ID NO:6).

[0012] In some of the examples described herein, the monoclonal antibody is not subject to prior lyophilization. In some of the examples described herein, the monoclonal antibody is a humanized antibody. In some

of the examples described herein, the monoclonal antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:7, and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:8. In some of the examples described herein, the monoclonal antibody is a full length antibody. In some of the examples described herein, the monoclonal antibody is an IgG1 antibody. In some of the examples described herein, the monoclonal antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:9, and a heavy comprising the amino acid sequence of SEQ ID NO: 10. In some of the examples described herein, the monoclonal antibody is stored in a glass vial or a metal alloy container. In some of the examples described herein, the metal alloy is 316L stainless steel or hastelloy. In some of the examples described herein, the formulation is stable at 2-8°C for at least 6 months. In some of the examples described herein, the formulation is stable at 2-8°C for at least 12 months. In some of the examples described herein, the formulation is stable at 2-8°C for at least 24 months. In some of the examples described herein, the antibody in the formulation retains at least about 80% of its biological activity after storage. In some of the examples described herein, the biological activity is measured by antibody binding to PD-L1. In some of the examples described herein, the formulation is sterile. In some of the examples described herein the formulation is suitable to be administered to a subject. In some of the examples described herein, the formulation is for subcutaneous administration.

[0013] Also provided herein is an article of manufacture comprising a container holding the liquid pharmaceutical formulation of any of the examples described above. In

some examples, the container is a glass vial or a metal alloy container. In some examples, the metal alloy is 316L stainless steel or hastelloy.

[0013a] In one aspect, the present disclosure refers to an article of manufacture comprising a container holding the liquid pharmaceutical formulation disclosed herein.

[0014] Also provided herein is a kit comprising a container holding the liquid pharmaceutical formulation of any of the examples described above.

[0014a] In one aspect, the present disclosure refers to a kit comprising a container holding the liquid pharmaceutical formulation disclosed herein.

[0015] Also provided herein is a method of treating a disease or disorder in a subject comprising administering an effective amount of the liquid pharmaceutical formulation of any of the examples described above to the subject, wherein the disease or disorder is selected from the group consisting of infection, cancer, and inflammatory disease. In some examples, the disease or disorder is cancer. In some examples, the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, urothelial carcinoma, and breast cancer. In some examples, the breast cancer is triple negative breast cancer. In some examples, the subject is a human.

[0015a] In one aspect, the present disclosure refers to use of the liquid pharmaceutical formulation disclosed herein in the manufacture of a medicament for treating a disease or disorder in a subject, wherein the disease or disorder is selected from the group consisting of infection, cancer, and inflammatory disease.

[0016] It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure. These and other examples of the disclosure will become apparent to one of skill in the art. These and other examples of the disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0018] FIG. 1A-1C shows the levels of high molecular weight species (HMWS) (FIG. 1A), ion exchange chromatography (IEC) main peak percentages (FIG. 1B), and non-reducing capillary electrophoresis-SDS (NR CE-SDS) pre-peak sums (FIG. 1C) of various drug substance (DS) formulations after multiple freeze/thaw cycles.

[0019] FIG. 2A-2C shows the levels of acidic species (FIG. 2A), basic species (FIG. 2B) and HMWS (FIG. 2C) of various DS formulations after up to 1 month at 25ºC.

CLAIMS

What is claimed is:

1. A liquid pharmaceutical formulation, the formulation comprising a monoclonal anti-PD-L1 antibody in a concentration of about 100 g/L to about 150 g/L, histidine acetate in a concentration of about 15 mM to about 25 mM, sucrose in a concentration of about 200 mM to about 280 mM, polysorbate in a concentration of about 0.04% (w/v) to about 0.08% (w/v), methionine in a concentration of about 5 mM to about 15 mM, and pH of about 5.6 to about 6.0, wherein the monoclonal antibody comprises

(a) a light chain variable region comprising:

(1) HVR-L1 comprising the amino acid sequence RASQDVSTAVA (SEQ ID NO: l);

(2) HVR-L2 comprising the amino acid sequence SASFLYS (SEQ ID NO:2);

(3) HVR-L3 comprising the amino acid sequence QQYLYHPAT (SEQ ID NO:3); and

(b) a heavy chain variable region comprising:

(1) HVR-H1 comprising the amino acid sequence GFTFSDSWIH (SEQ ID NO:4);

(2) HVR-H2 comprising the amino acid sequence AWISPYGGSTYYADSVKG (SEQ ID NO:5);

(3) HVR-H3 comprising the amino acid sequence WPGGFDY (SEQ ID NO:6).

2. The liquid pharmaceutical formulation of claim 1, wherein the monoclonal antibody in the formulation is in a concentration of about 120 g/L to about 130 g/L.

3. The liquid pharmaceutical formulation of claim 1, wherein the monoclonal antibody in the formulation is in a concentration of about 125 g/L.

4. The liquid pharmaceutical formulation of any one of claims 1-3, wherein the histidine acetate is in a concentration of about 17 mM to about 22 mM.

5. The liquid pharmaceutical formulation of any one of claims 1-3, wherein the histidine acetate is in a concentration of about 20 mM.

6. The liquid pharmaceutical formulation of any one of claims 1-5, wherein the sucrose is in a concentration of about 220 mM to about 260 mM.

7. The liquid pharmaceutical formulation of any one of claims 1-5, wherein the sucrose is in a concentration of about 240 mM.

8. The liquid pharmaceutical formulation of any one of claims 1-7, wherein the pH is about 5.8.

9. The liquid pharmaceutical formulation of any one of claims 1-8, wherein the polysorbate in the formulation is polysorbate 20.

10. The liquid pharmaceutical formulation of any one of claims 1-9, wherein the polysorbate is in a concentration of about 0.05% (w/v) to about 0.07% (w/v).

11. The liquid pharmaceutical formulation of any one of claims 1-9, wherein the polysorbate is in a concentration of about 0.06% (w/v).

12. The liquid pharmaceutical formulation of any one of claims 1-11, wherein the methionine is in a concentration of about 10 mM.

13. The liquid pharmaceutical formulation of any one of claims 1-12, wherein the formulation further comprises a hyaluronidase enzyme.

14. The liquid pharmaceutical formulation of claim 13, wherein the hyaluronidase enzyme is recombinant human hyaluronidase (rHuPH20).

15. The liquid pharmaceutical formulation of claim 13 or 14, wherein the hyaluronidase enzyme is in a concentration of about 1000 U/ml to about 3000 U/ml.

16. The liquid pharmaceutical formulation of claim 13 or 14, wherein the hyaluronidase enzyme is in a concentration of about 2000 U/ml.

17. A liquid pharmaceutical formulation, the formulation comprising a monoclonal anti-PD-L1 antibody in a concentration of about 100 g/L to about 150 g/L, histidine acetate in a concentration of about 15 mM to about 25 mM, sucrose in a concentration of about 200 mM to about 280 mM, polysorbate in a concentration of about 0.01% (w/v) to about 0.03% (w/v), and pH of about 5.3 to about 5.7, wherein the monoclonal antibody comprises

(a) a light chain variable region comprising:

(1) HVR-L1 comprising the amino acid sequence RASQDVSTAVA (SEQ ID NO: 1);

(2) HVR-L2 comprising the amino acid sequence SASFLYS (SEQ ID NO:2);

(3) HVR-L3 comprising the amino acid sequence QQYLYHPAT (SEQ ID NO:3); and

(b) a heavy chain variable region comprising:

(1) HVR-H1 comprising the amino acid sequence GFTFSDSWIH (SEQ ID NO:4);

(2) HVR-H2 comprising the amino acid sequence AWISPYGGSTYYADSVKG (SEQ ID NO:5);

(3) HVR-H3 comprising the amino acid sequence WPGGFDY (SEQ ID NO:6).

18. The liquid pharmaceutical formulation of claim 17, wherein the monoclonal antibody in the formulation is in a concentration of about 120 g/L to about 130 g/L.

19. The liquid pharmaceutical formulation of claim 17, wherein the monoclonal antibody in the formulation is in a concentration of about 125 g/L.

20. The liquid pharmaceutical formulation of any one of claims 17-19, wherein the histidine acetate is in a concentration of about 17 mM to about 22 mM.

21. The liquid pharmaceutical formulation of any one of claims 17-19, wherein the histidine acetate is in a concentration of about 20 mM.

22. The liquid pharmaceutical formulation of any one of claims 17-21, wherein the sucrose is in a concentration of about 220 mM to about 260 mM.

23. The liquid pharmaceutical formulation of any one of claims 17-21, wherein the sucrose is in a concentration of about 240 mM.

24. The liquid pharmaceutical formulation of any one of claims 17-23, wherein the pH is about 5.5.

25. The liquid pharmaceutical formulation of any one of claims 17-24, wherein the polysorbate in the formulation is polysorbate 20.

26. The liquid pharmaceutical formulation of any one of claims 17-25, wherein the polysorbate is in a concentration of about 0.02% (w/v).

27. The liquid pharmaceutical formulation of any one of claims 17-26, wherein the formulation is mixed with a hyaluronidase enzyme prior to being administered to a subject.

28. The liquid pharmaceutical formulation of claim 27, wherein the hyaluronidase enzyme is recombinant human hyaluronidase (rHuPH20).

29. The liquid pharmaceutical formulation of claim 27 or 28, wherein the hyaluronidase enzyme concentration in the mixture is about 1000 U/ml to about 3000 U/ml.

30. The liquid pharmaceutical formulation of claim 27 or 28, wherein the hyaluronidase enzyme concentration in the mixture is about 2000 U/ml.

31. The liquid pharmaceutical formulation of any one of claims 1-30, wherein the monoclonal antibody is not subject to prior lyophilization.

32. The liquid pharmaceutical formulation of any one of claims 1-31, wherein the monoclonal antibody is a humanized antibody.

33. The liquid pharmaceutical formulation of any one of claims 1-32, wherein the monoclonal antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:7, and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:8.

34. The liquid pharmaceutical formulation of any one of claims 1-33, wherein the monoclonal antibody is a full length antibody.

35. The liquid pharmaceutical formulation of claim 34, wherein the monoclonal antibody is an IgG1 antibody.

36. The liquid pharmaceutical formulation of any one of claims 1-35, wherein the monoclonal antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:9, and a heavy comprising the amino acid sequence of SEQ ID NO: 10.

37. The liquid pharmaceutical formulation of any one of claims 1-36, wherein the monoclonal antibody is stored in a glass vial or a metal alloy container.

38. The liquid pharmaceutical formulation of claim 37, wherein the metal alloy is 316L stainless steel or hastelloy.

39. The liquid pharmaceutical formulation of any one of claims 1-38, wherein the formulation is stable at 2-8°C for at least 6 months.

40. The liquid pharmaceutical formulation of any one of claims 1-38, wherein the formulation is stable at 2-8°C for at least 12 months.

41. The liquid pharmaceutical formulation of any one of claims 1-38, wherein the formulation is stable at 2-8°C for at least 24 months.

42. The liquid pharmaceutical formulation of any one of claims 39-41, wherein the antibody in the formulation retains at least about 80% of its biological activity after storage.

43. The liquid pharmaceutical formulation of claim 42, wherein the biological activity is measured by antibody binding to PD-L1.

44. The liquid pharmaceutical formulation of any one of claims 1-43, wherein the formulation is sterile.

45. The liquid pharmaceutical formulation of any one of claims 1-44, wherein the formulation is suitable to be administered to a subject.

46. The liquid pharmaceutical formulation of any one of claims 1-45, wherein the formulation is for subcutaneous administration.

47. An article of manufacture comprising a container holding the liquid pharmaceutical formulation of any one of claims 1-46.

48. The article of manufacture of claim 47, wherein the container is a glass vial or a metal alloy container.

49. The article of manufacture of claim 48, wherein the metal alloy is 316L stainless steel or hastelloy.

50. A kit comprising a container holding the liquid pharmaceutical formulation of any one of claims 1-46.

51. Use of the liquid pharmaceutical formulation of any one of claims 1-46 in the manufacture of a medicament for treating a disease or disorder in a subject, wherein the disease or disorder is selected from the group consisting of infection, cancer, and inflammatory disease.

52. The use of claim 51, wherein the disease or disorder is cancer.

53. The use of claim 52, wherein the cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, urothelial carcinoma, and breast cancer.

54. The use of claim 53, wherein the breast cancer is triple negative breast cancer.

55. The use of any one of claims 51-54, wherein the subject is a human.