SUMMARY

[0008] Provided herein are stable aqueous pharmaceutical formulations comprising an antibody. The formulation comprises an antibody (e.g., an anti-PDL1 antibody), a buffer, sucrose, and a surfactant, wherein the formulation has a pH of about 5.0 to about 7.0.

[0009] In one example, provided herein is a stable aqueous pharmaceutical formulation, the formulation comprising an anti-PDL1 monoclonal antibody in a concentration of about 40 mg/ml to about 125 mg/ml, histidine acetate or sodium acetate in a concentration of about 15 mM to about 25 mM, sucrose in a concentration of about 60 mM to about 240 mM, polysorbate in a concentration of about 0.005% (w/v) to about 0.06% (w/v), and pH about 5.0 to about 6.3.

[0010] In some examples, the monoclonal antibody in the formulation is about 40 mg/ml to about 80 mg/ml. In some examples, the monoclonal antibody in the formulation is about 54 mg/ml to about 66 mg/ml. In some examples, the monoclonal antibody in the formulation is about 60 mg/ml. In some examples, the monoclonal antibody in the formulation is about 60 mg/ml to about 125 mg/ml. In some examples, the monoclonal antibody in the formulation is about 125 mg/ml.

[0011] In some examples, said histidine acetate or sodium acetate in the formulation is in a concentration of about 17 mM to about 22 mM. In some examples, said histidine acetate or sodium acetate in the formulation is in a concentration of about 20 mM.

[0012] In some examples, said sucrose in the formulation is about 60 mM to about 180 mM. In some examples, said sucrose in the formulation is about 120 mM. In some examples, said sucrose in the formulation is about 240 mM.

[0013] In some examples, the formulation has a pH of about 5.5 to about 6.1. In some examples, the formulation has a pH of about 5.5 or about 5.8.

[0014] In some examples, said polysorbate in the formulation is polysorbate 20. In some examples, said polysorbate (e.g., polysorbate 20) in the formulation is about 0.02% to about 0.04%.

[0015] In some examples, said monoclonal antibody in the formulation is about 60 mg/ml, sucrose in the formulation is about 120 mM, and pH is about 5.8. In some examples, said monoclonal antibody in the formulation is about 125 mg/ml, sucrose in the formulation is about 240 mM, and pH is about 5.5.

[0016] In some examples, the formulation comprises a monoclonal antibody (e.g., an anti-PDL1 antibody described herein) in an amount of about 60 mg/mL, histidine acetate in a concentration of about 20 mM, sucrose in a concentration of about 120 mM, and polysorbate

which is polysorbate 20 in a concentration of 0.04% (w/v), and the formulation has a pH of about 5.8.

[0017] In some examples, the formulation comprises a monoclonal antibody in an amount of about 125 mg/mL, histidine acetate in a concentration of about 20 mM, sucrose in a concentration of about 240 mM, and polysorbate which is polysorbate 20 in a concentration of 0.02%, and the formulation has a pH of about 5.5.

[0018] In some examples, said monoclonal antibody in the formulation is not subject to prior lyophilization. In some examples, said monoclonal antibody in the formulation is a full length antibody. In some examples, said monoclonal antibody in the formulation is an IgG1 antibody. In some examples, said monoclonal antibody in the formulation is a humanized antibody. In some examples, said monoclonal antibody in the formulation is an antibody fragment comprising an antigen-binding region. In some examples, the antibody fragment is a Fab or $F(ab')_2$ fragment.

[0019] In some examples, said monoclonal antibody in the formulation 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 RHWPGGFDY (SEQ ID NO:6).

[0020] In some examples, said monoclonal antibody in the formulation 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 examples, said monoclonal antibody in the formulation comprises a light chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the light chain variable region having the amino acid sequence of SEQ ID NO:7, and a heavy chain variable region having at least 85% , 86%,

87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the heavy chain variable region having the amino acid sequence of SEQ ID NO:8. In some examples, said monoclonal antibody in the formulation 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:32. In some examples, said monoclonal antibody in the formulation comprises a light chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the light chain variable region having the amino acid sequence of SEQ ID NO:7, and a heavy chain variable region having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the heavy chain variable region having the amino acid sequence of SEQ ID NO:32. In some examples, said monoclonal antibody in the formulation 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 examples, said monoclonal antibody in the formulation comprises a light chain having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the light chain having the amino acid sequence of SEQ ID NO:9, and a heavy chain having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the heavy chain having the amino acid sequence of SEQ ID NO:10.

[0021] In some examples, the formulation comprising the antibody is stored in a glass vial or a metal alloy container. In some examples, the metal alloy is 316L stainless steel or hastelloy. In some examples, the formulation is stable at 2-8ºC for at least 6 months, at least 12 months, at least 18 months or at least 24 months. In some examples, the antibody in the formulation retains, after storage, at least about 75%, at least about 80%, at least about 85%, at least about 90% of the biological activity before storage. In some examples, the biological activity is measured by antibody binding to PD-L1.

[0022] In some examples, the formulation described herein is sterile. In some examples, the formulation described herein is suitable to be administered to a subject. In some examples, the formulation described herein is for intravenous (IV) administration.

[0023] In another example, provided herein is an article of manufacture or kit comprising a container holding any of the stable aqueous pharmaceutical formulation described above and herein. 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.

[0024] In another example, provided herein is a method of treating a disease or disorder in a subject comprising administering an effective amount of the formulation described herein to the subject, wherein the disease or disorder is selected from the group consisting of infection, cancer, and inflammatory disease.

[0024a] In one aspect, the present disclosure refers to use of a stable aqueous pharmaceutical formulation in the manufacture of a medicament for treating cancer in a subject, said formulation comprising an anti-PDL1 monoclonal antibody in a concentration of 40 mg/ml to 125 mg/ml, histidine acetate or sodium acetate in a concentration of 15 mM to 25 mM, sucrose in a concentration of 60 mM to 240 mM, polysorbate in a concentration of 0.005% (w/v) to 0.06% (w/v), and pH 5.0 to 6.3, wherein said 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 RHWPGGFDY (SEQ ID NO:6), wherein the cancer is selected from the group consisting of a solid tumor, a hematologic cancer, bladder cancer, brain cancer, breast cancer, colon cancer, colorectal cancer, gastric cancer, glioma, head cancer, leukemia, liver cancer, lung cancer, lymphoma, myeloma, neck cancer, ovarian cancer, melanoma, pancreatic cancer, renal cancer, salivary cancer, stomach cancer, thymic epithelial cancer, thyroid cancer, and squamous cell carcinoma of the head and neck.

[0025] 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 aspects 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

[0026] **FIG. 1** is a series of graphs showing statistical analysis of stability data of α-PDL1 formulations at 40°C by ICIEF using JMP software. **A)** Average main peak rate loss from fractional factorial design of experiments (DOE). **B)** Main peak analysis from fractional factorial DOE. Main peak contains α-PDL1 charged species with the same pH as the pI (isoelectric point) of the molecule.

[0027] **FIG. 2** is a series of graphs showing statistical analysis of stability data of α-PDL1 formulations at 25°C by ICIEF using JMP software. **A)** Average main peak rate loss from fractional factorial design of experiments (DOE). **B)** Main peak analysis from fractional factorial DOE. Main peak contains α-PDL1 charged species with the same pH as the pI (isoelectric point) of the molecule.

[0028] **FIG. 3** is a series of graphs showing statistical analysis of stability data of α-PDL1 formulations at 40°C by SE-HPLC using JMP software. **A)** Average main peak rate loss from fractional factorial design of experiments (DOE). **B)** Main peak analysis from fractional factorial DOE. Main peak contains α-PDL1 monomer.

[0029] **FIG. 4** is a series of graphs showing statistical analysis of stability data of α-PDL1 formulations at 25°C by SE-HPLC using JMP software. **A)** Average main peak rate loss from fractional factorial design of experiments (DOE). **B)** Main peak analysis from fractional factorial DOE. Main peak contains α-PDL1 monomer.

[0030] **FIG. 5** is a graph showing lack of significant PS20 degradation of various α-PDL1 formulations stored at various temperatures and time. Graph of percent (%) PS20 remaining in the formulation as detected by evaporative light scattering detector (ELSD) in F1 through

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a stable aqueous pharmaceutical formulation in the manufacture of a medicament for treating cancer in a subject, said formulation comprising an anti-PDL1 monoclonal antibody in a concentration of 40 mg/ml to 125 mg/ml, histidine acetate or sodium acetate in a concentration of 15 mM to 25 mM, sucrose in a concentration of 60 mM to 240 mM, polysorbate in a concentration of 0.005% (w/v) to 0.06% (w/v), and pH 5.0 to 6.3, wherein said 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 RHWPGGFDY (SEQ ID NO:6), wherein the cancer is selected from the group consisting of a solid tumor, a hematologic cancer, bladder cancer, brain cancer, breast cancer, colon cancer, colorectal cancer, gastric cancer, glioma, head cancer, leukemia, liver cancer, lung cancer, lymphoma, myeloma, neck cancer, ovarian cancer, melanoma, pancreatic cancer, renal cancer, salivary cancer, stomach cancer, thymic epithelial cancer, thyroid cancer, and squamous cell carcinoma of the head and neck.

2. The use of claim 1, wherein said monoclonal antibody is in a concentration of 60 mg/ml, sucrose is in a concentration of 120 mM, and pH is 5.8.

3. The use of claim 1, wherein said monoclonal antibody is in a concentration of 125 mg/ml, sucrose is in a concentration of 240 mM, and pH is 5.5.

4. The use of any one of claims 1-3, wherein said 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:32.

5. The use of any one of claims 1-4, wherein said monoclonal antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:9, and a heavy chain comprising the amino acid sequence of SEQ ID NO:10.

6. The use of claim 1, wherein said monoclonal antibody is in a concentration of 60 mg/mL, said histidine acetate is in a concentration of 20 mM, said sucrose is in a concentration of 120 mM, and said polysorbate is polysorbate 20 in a concentration of 0.04% (w/v), and said formulation has a pH of 5.8.

7. The use of claim 6, wherein said 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:32.

8. The use of claim 6, wherein said monoclonal antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:9, and a heavy chain comprising the amino acid sequence of SEQ ID NO:10.

9. The use of claim 1, wherein said monoclonal antibody is in a concentration of 125 mg/mL, said histidine acetate is in a concentration of 20 mM, said sucrose is in a concentration of 240 mM, and said polysorbate is polysorbate 20 in a concentration of 0.02%, and said formulation has a pH of 5.5.

10. The use of claim 9, wherein said 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:32.

11. The use of claim 9, wherein said monoclonal antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:9, and a heavy chain comprising the amino acid sequence of SEQ ID NO:10.

12. The use of any one of claims 1-11, wherein the formulation is for intravenous (IV) administration.

13. The use of any one of claims 1-12, wherein the cancer is locally advanced or metastatic.

14. The use of any one of claims 1-13, wherein the cancer is bladder cancer.

15. The use of any one of claims 1-13, wherein the cancer is lung cancer.

16. The use of claim 15, wherein the lung is non-small cell lung cancer.

17. The use of any one of claims 1-13, wherein the cancer is breast cancer.

18. The use of any one of claims 1-17, wherein the subject has PDL1 positive cancer.

19. The use of any one of claims 1-18, wherein the formulation is to be administered in conjunction with another therapeutic agent to the subject.

20. The use of claim 19, wherein the therapeutic agent is a chemotherapeutic agent or an antibody treatment.