

CLAIMS

What is claimed:

1. A stable aqueous pharmaceutical composition comprising:
 - a) about 44mg/mL to about 56 mg/mL of a bispecific epidermal growth factor receptor (EGFR)/hepatocyte growth factor receptor (c-Met) antibody, the bispecific antibody comprising:
 - a first heavy chain (HC1) comprising a HC1 variable region 1 (VH1);
 - a first light chain (LC1) comprising a light chain variable region 1 (VL1);
 - a second heavy chain (HC2) comprising a HC2 variable region 2 (VH2); and
 - a second light chain (LC2) comprising a light chain variable region 2 (VL2),wherein the VH1 comprises a heavy chain complementarity determining region 1 (HCDR1), a HCDR2 and a HCDR3 amino acid sequences of SEQ ID NOs: 1, 2, and 3, respectively; the VL1 comprises a light chain complementarity determining region 1 (LCDR1), a LCDR2 and a LCDR3 amino acid sequences of SEQ ID NOs: 4, 5 and 6, respectively, the VH2 comprises the HCDR1, the HCDR2 and the HCDR3 amino acid sequences of SEQ ID NOs: 7, 8 and 9, respectively; and the VL2 comprises the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 10, 11 and 12, respectively;
 - b) about 8 mM to about 12 mM of histidine and/or pharmaceutically acceptable histidine salt,
 - c) about 6.8% (w/v) to about 10.2% (w/v) of sucrose,
 - d) about 0.036% (w/v) to about 0.084% (w/v) of polysorbate 80 (PS80),
 - e) about to 0.8 mg/mL to about 1.2 mg/mL of methionine,
 - f) about 16 µg/mL to about 24 µg/mL of ethylenediaminetetraacetic acid (EDTA); and
 - g) a pH from about 5.2 to about 6.2.
2. The stable aqueous pharmaceutical composition of claim 1, wherein the bispecific EGFR-cMet antibody comprises an HC1 variable region comprising the amino acid sequence of SEQ ID NO:13 and a LC1 variable region comprising the amino acid sequence of SEQ ID NO:14.
3. The stable aqueous pharmaceutical composition of claim 1 or claim 2, wherein the bispecific EGFR-cMet antibody comprises a HC2 variable region comprising the amino acid sequence of SEQ ID NO:15 and a LC2 variable region comprising the amino acid sequence of SEQ ID NO:16.

4. The stable aqueous pharmaceutical composition of any one of claims 1-3, wherein the HC1 comprises the amino acid sequence of SEQ ID NO:17 and the LC1 comprises the amino acid sequence of SEQ ID NO:18.
5. The stable aqueous pharmaceutical composition of any one of claims 1-4, wherein the HC2 comprises the amino acid sequence of SEQ ID NO:19 and the LC2 comprises the amino acid sequence of SEQ ID NO:20.
6. The stable aqueous pharmaceutical composition of any one of claims 1-5, wherein the bispecific EGFR-cMet antibody is amivantamab.
7. The stable aqueous pharmaceutical composition of any one of claims 1-6, wherein the bispecific EGFR-cMet antibody has a concentration of about 50 mg/mL.
8. The stable aqueous pharmaceutical composition of any one of claims 1-7, wherein the histidine and/or pharmaceutically acceptable histidine salt has a concentration of about 10 mM.
9. The stable aqueous pharmaceutical composition of any one of claims 1-8, wherein the histidine and/or pharmaceutically acceptable histidine salt comprises L-histidine and L-histidine hydrochloride monohydrate.
10. The stable aqueous pharmaceutical composition of any one of claims 1-9, comprising about 8.5% (w/v) sucrose.
11. The stable aqueous pharmaceutical composition of any one of claims 1-10, comprising about 0.06% (w/v) PS80.
12. The stable aqueous pharmaceutical composition of any one of claims 1-11, wherein the methionine has a concentration of about 1 mg/mL.
13. The stable aqueous pharmaceutical composition of any one of claims 1-12, wherein the EDTA has a concentration of about 20 µg/mL.
14. The stable aqueous pharmaceutical composition of any one of claims 1-13, wherein the pH is about 5.7.
15. The stable aqueous pharmaceutical composition of any one of claims 1-14, comprising 50 mg/mL of the bispecific EGFR-cMet antibody, 10 mM histidine and/or pharmaceutically acceptable histidine salt, 8.5% (w/v) sucrose, 0.06% (w/v) PS80, 1 mg/mL methionine, and 20 µg/mL EDTA.
16. The stable aqueous pharmaceutical composition of any one of claims 1-15 wherein the stable aqueous pharmaceutical composition is stable at a temperature of about 2-8° C for at least two years.

17. The stable aqueous pharmaceutical composition of any one of claims 1-16, wherein stability is defined based on color of solution, pH, turbidity, number of subvisible particles, percentage of aglycosylated heavy chain (AGHC), percentage of new peak(s), percentage of high molecular weight species (HMWS), percentage of low molecular weight species (LMWS), percentage of sum of acidic peaks, percentage of sum of basic peaks, protein concentration, percentage of EGFR binding activity, percentage of cMet binding activity, percentage of PS80, or any combination thereof.
18. The stable aqueous pharmaceutical composition of any one of claims 1-17, wherein the total volume of the composition ranges from about 5mL to about 10mL.
19. ~~A method of treating cancer in a subject in need thereof, the method comprising administering to the subject the~~Use of a pharmaceutical composition of any one of claims 1-18 in the manufacture of a medicament for the treatment of cancer, wherein the pharmaceutical composition is to be administered to a subject in need thereof.
20. The ~~method-use of claim 19, wherein the administering pharmaceutical composition is to be administered intravenously.~~is intravenous.
21. A method for preparing a stable aqueous pharmaceutical composition of a bispecific antibody targeting EGFR and cMet, the bispecific antibody targeting EGFR and cMet comprising a first heavy chain (HC1) comprising a HC1 variable region 1 (VH1); a first light chain (LC1) comprising a light chain variable region 1 (VL1); a second heavy chain (HC2) comprising a HC2 variable region 2 (VH2); and a second light chain (LC2) comprising a light chain variable region 2 (VL2), wherein the VH1 comprises a heavy chain complementarity determining region 1 (HCDR1), a HCDR2 and a HCDR3 comprising amino acid sequences of SEQ ID NOs: 1, 2, and 3, respectively; the VL1 comprises a light chain complementarity determining region 1 (LCDR1), a LCDR2 and a LCDR3 comprising amino acid sequences of SEQ ID NOs: 4, 5 and 6, respectively; the VH2 comprises HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NOs: 7, 8 and 9, respectively; and the VL2 comprises LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs: 10, 11 and 12, respectively; the method comprising: combining a composition comprising about 50 mg/mL of the bispecific antibody, about 10 mM histidine and/or pharmaceutically acceptable histidine salt, about 8.5% Sucrose, and about 1 mg/mL L-methionine with polysorbate 80 to a final concentration of about 0.06% (w/v) and EDTA to a final concentration of about 20 µg/mL, wherein the stable aqueous pharmaceutical composition has about pH 5.7.

22. The method of claim 21, wherein the bispecific EGFR-cMet antibody comprises an HC1 variable region comprising the amino acid sequence of SEQ ID NO:13 and a LC1 variable region comprising the amino acid sequence of SEQ ID NO:14.
23. The method of any one of claims 21-22, wherein the bispecific EGFR-cMet antibody comprises a HC2 variable region comprising the amino acid sequence of SEQ ID NO:15 and a LC2 variable region comprising the amino acid sequence of SEQ ID NO:16.
24. The method of any one of claims 21-23, wherein the antibody comprises a heavy chain 1 (HC1) comprising the amino acid sequence of SEQ ID NO:17 and a light chain 1 (LC1) comprising the amino acid sequence of SEQ ID NO:18.
25. The method of any one of claims 21-24, wherein the antibody comprises a HC2 comprising the amino acid sequence of SEQ ID NO:19 and a LC2 comprising the amino acid sequence of SEQ ID NO:20.
26. The method of any one of claims 21-25, wherein the antibody is amivantamab.
27. A kit comprising the stable aqueous pharmaceutical composition of any one of claims 1-18 and instructions for use thereof.
28. An article of manufacture comprising a container holding a stable aqueous pharmaceutical composition in accordance with any one of claims 1-18.
29. The article of manufacture according to claim 28, wherein the container is a vial with a stopper pierceable by a syringe.
30. A pharmaceutical composition of any one of claims 1-18 for use in the treatment of cancer.
31. A pharmaceutical composition of any one of claims 1-18 for use in the preparation of a medicine.
- ~~32. Use of a pharmaceutical composition for treating cancer in a subject in need thereof by administering the pharmaceutical composition of any one of claims 1-18.~~
~~Use of a pharmaceutical composition according to claim 32, wherein the administration is intravenous.~~