International Patent Application Publication No. WO 2016/082044 describes dosing regimens for anti-HER2 biparatopic antibodies.

[0005] International Patent Application Publication No. WO 2019/173911 describes anti-HER2 biparatopic antibody-drug conjugates comprising an auristatin analogue.

[0006] Most marketed antibody-based therapeutics are administered to subjects in dosages based either on the weight or the body surface area of a subject. For example, a therapeutic antibody may be administered at a dosage of *X* mg/kg of body weight, or *Y* mg/m^2 of body surface area. For example, the monoclonal antibody panitumumab has been approved has been approved for administration at a dosage of 6mg/kg every 2 weeks (Q2W) and the monoclonal antibody nivolumab has been approved for administration at a dosage of 3 mg/kg Q2W. The monoclonal antibody rituximab has been approved for administration at a dosage of 375 mg/m^2 body surface area. The monoclonal antibody cetuximab has been approved for administration at a dosage of 250 mg/m^2 body surface area every week after a loading dose of 400 mg/m^2. Recently, the administration of therapeutic antibodies at fixed dosages (independent of body weight or body surface area) has been suggested (Hendrikx, J. et al., Fixed Dosing of Monoclonal Antibodies in Oncology, The Oncologist 22:1212 (2017)).

[0007] This background information is provided for the purpose of making known information believed by the applicant to be of possible relevance to the present disclosure. No admission is necessarily intended, nor should be construed, that any of the preceding information constitutes prior art against the claimed invention.

SUMMARY

[0008] Described herein are methods of treating cancer using anti-HER2 biparatopic antibodies. In one example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject an effective amount of an anti-HER2 biparatopic antibody at a fixed time interval, the effective amount comprising a fixed dose of the antibody administered.

[0008a] In one aspect, provided herein is the use of an anti-HER2 biparatopic antibody in the manufacture of a medicament for treating a HER2-expressing cancer in a subject, wherein an

effective amount of the medicament is to be administered to the subject, wherein the effective amount is to be administered according to a 2-tiered fixed dosing regimen comprising a low fixed dose to be administered at a fixed time interval to a subject whose weight is less than a dose cut-off weight, and a high fixed dose to be administered at a fixed time interval to a subject whose weight is equal to or greater than the dose cut-off weight, wherein the anti-HER2 biparatopic antibody comprises: (a) a first antigen-binding domain comprising CDR sequences CDRH1, CDRH2 and CDRH3 as set forth in SEQ ID NOs: 32, 34 and 33 respectively, and CDR sequences CDRL1, CDRL2 and CDRL3 as set forth in SEQ ID NOs: 22, 24 and 23 respectively, and (b) a second antigen-binding domain comprising CDR sequences CDRH1, CDRH2 and CDRH3 as set forth in SEQ ID NOs: 56, 57 and 58 respectively, and CDR sequences CDRL1, CDRL2 and CDRL3 as set forth in SEQ ID NOs: 53, 54 and 55 respectively, and wherein: (i) the low fixed dose is about 1200 mg and the high fixed dose is about 1600 mg, the dose cut-off weight is 70 kg and the fixed time interval is every 2 weeks (Q2W), or (ii) the low fixed dose is about 1800 mg and the high fixed dose is about 2400 mg, the dose cut-off weight is 70 kg and the fixed time interval is every 3 weeks (Q3W).

[0009] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject, at a fixed time interval, an

effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a two-tiered fixed dose, wherein a low fixed dose is administered to a subject weighing less than a weight cutoff point, and a high fixed dose is administered to a subject weighing at or above the weight cutoff point.

[0010] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject, at a fixed time interval, an effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a two-tiered fixed dose, wherein a low fixed dose is administered to a subject weighing less than 70kg, and a high fixed dose is administered to a subject weighing 70kg or more.

[0011] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject an effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a fixed dose of 1800 mg to a subject weighing less than 70kg, or a fixed dose of 2400 mg to a subject weighing 70 kg or more, wherein the dose is administered every 3 weeks (Q3W).

[0012] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject an effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a fixed dose of 1800 mg to a subject weighing less than 70kg, or a fixed dose of 2400 mg to a subject weighing 70 kg or more, wherein the dose is administered every 3 weeks (Q3W) wherein the HER2 biparatopic antibody comprises (a) a first antigen-binding domain comprising a variable heavy chain region (VH) comprising the sequence as set forth in SEQ ID NO: 31, and a variable light chain region (VL) comprising the sequence as set forth in SEQ ID NO: 21, and (b) a second antigen-binding domain comprising a VH sequence as set forth in SEQ ID NO: 52, and a VL sequence as set forth in SEQ ID NO: 51.

[0013] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject an effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a fixed dose of 1800 mg to a subject weighing less than 70kg, or a fixed dose of 2400 mg to a subject weighing 70kg or more, wherein the dose is administered every 3 weeks (Q3W), wherein the subject has been diagnosed with breast cancer, gastroesophageal adenocarcinoma (GEA), esophageal cancer, gastric cancer, endometrial

cancer, ovarian cancer, cervical cancer, non-small cell lung cancer (NSCLC), anal cancer, colorectal cancer (CRC) or biliary tract cancer.

[0014] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject an effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a fixed dose of 1800 mg to a subject weighing less than 70kg, or a fixed dose of 2400 mg to a subject weighing 70kg or more, wherein the dose is administered every 3 weeks (Q3W), wherein the subject has been diagnosed with gastroesophageal adenocarcinoma (GEA), esophageal cancer, gastroesophageal junction cancer (GEJ), or gastric cancer..

[0015] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject an effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a fixed dose of 1200 mg to a subject weighing less than 70kg, or a fixed dose of 1600 mg to a subject weighing 70 kg or more, wherein the dose is administered every 2 weeks (Q2W).

[0016] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject an effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a fixed dose of 1200 mg to a subject weighing less than 70kg, or a fixed dose of 1600 mg to a subject weighing 70 kg or more, wherein the dose is administered every 2 weeks (Q2W), wherein the subject has been diagnosed with biliary tract cancer.

[0017] In another example, the present disclosure relates to a method of treating a subject having a HER2-expressing cancer comprising administering to the subject an effective amount of an anti-HER2 biparatopic antibody, the effective amount comprising a fixed dose of 1200 mg to a subject weighing less than 70kg, or a fixed dose of 1600 mg to a subject weighing 70 kg or more, wherein the dose is administered every 2 weeks (Q2W) wherein the HER2 biparatopic antibody comprises (a) a first antigen-binding domain comprising a variable heavy chain region (VH) comprising the sequence as set forth in SEQ ID NO: 31, and a variable light chain region (VL) comprising the sequence as set forth in SEQ ID NO: 21, and (b) a second antigen-binding domain comprising a VH sequence as set forth in SEQ ID NO: 52, and a VL sequence as set forth in SEQ ID NO: 51.

In another example, the present disclosure relates to a a pharmaceutical kit comprising: (i) one or more containers comprising an anti-HER-2 biparatopic antibody and (ii) a label or package insert in or associated with the one or more containers indicating that the anti-HER2 biparatopic antibody is for administration to a subject having a HER2-expressing cancer (a) at a dose of 1800mg for a subject weighting less than 70kg or (b) at a dose of 2400mg for a subject weighing 70kg or more, administered every 3 weeks (Q3W).

In another example, the present disclosure relates to a pharmaceutical kit comprising an anti-HER-2 biparatopic antibody and (ii) a label or package insert in or associated with the one or more containers indicating that the anti-HER2 biparatopic antibody is for administration to a subject having a HER2-expressing cancer (a) at a dose of 1200mg for a subject weighting less than 70kg or (b) at a dose of 1600mg for a subject weighing 70kg or more, administered every 2 weeks (Q2W).

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] **Figure 1** shows a schematic representation of the anti-HER2 biparatopic antibody v10000.

[0019] **Figure 2** shows a visual predictive check of median predicted exposure (solid line), 95% prediction interval (grey band) compared to observed data (open circles), median observed concentration (dotted line), and observed 2.5th/97.5th percentiles (dashed lines) for various dosing regimens. **Figure 2A**, dose of 5 mg/kg administered weekly (QW). **Figure 2B**, dose of 10 mg/kg administered weekly (Q2W). **Figure 2C**, dose of 20 mg/kg administered every 2 weeks (Q2W). **Figure 2D**, dose of 30 mg/kg administered every 3 weeks (Q3W).

[0020] **Figure 3** shows model-predicted AUC at steady state by body weight using several dosing regimens. **Figure 3A**, weight-based (30mg/kg Q3W) dosing. **Figure 3B**, one-tiered (2100mg Q3W) flat dosing; **Figure 3C**, two-tiered flat dosing (1800/2400 mg Q3W). The two-tiered flat dose (1800/2400 mg Q3W) is administered as 1800 mg to patients below 70 kg, and 2400 mg to patients above 70 kg.

[0021] **Figure 4** is a schematic showing the design of the clinical study described in Example 4 of v10000 in the treatment of gastrointestinal cancers. 5-FU = 5-fluorouracil; DCR = disease

WE CLAIM:

1. Use of an anti-HER2 biparatopic antibody in the manufacture of a medicament for treating a HER2-expressing cancer in a subject, wherein an effective amount of the medicament is to be administered to the subject,

wherein the effective amount is to be administered according to a 2-tiered fixed dosing regimen comprising a low fixed dose to be administered at a fixed time interval to a subject whose weight is less than a dose cut-off weight, and a high fixed dose to be administered at a fixed time interval to a subject whose weight is equal to or greater than the dose cut-off weight,

wherein the anti-HER2 biparatopic antibody comprises: (a) a first antigen-binding domain comprising CDR sequences CDRH1, CDRH2 and CDRH3 as set forth in SEQ ID NOs: 32, 34 and 33 respectively, and CDR sequences CDRL1, CDRL2 and CDRL3 as set forth in SEQ ID NOs: 22, 24 and 23 respectively, and (b) a second antigen-binding domain comprising CDR sequences CDRH1, CDRH2 and CDRH3 as set forth in SEQ ID NOs: 56, 57 and 58 respectively, and CDR sequences CDRL1, CDRL2 and CDRL3 as set forth in SEQ ID NOs: 53, 54 and 55 respectively,

and wherein: (i) the low fixed dose is about 1200 mg and the high fixed dose is about 1600 mg, the dose cut-off weight is 70 kg and the fixed time interval is every 2 weeks (Q2W), or (ii) the low fixed dose is about 1800 mg and the high fixed dose is about 2400 mg, the dose cut-off weight is 70 kg and the fixed time interval is every 3 weeks (Q3W).

2. The use according to Claim 1, wherein the first antigen-binding domain is a Fab and the second antigen-binding domain is an scFv.

3. The use according to Claim 1 or 2, wherein (a) the first antigen-binding domain comprises a variable heavy chain region (VH) comprising the sequence as set forth in SEQ ID NO: 31, and a variable light chain region (VL) comprising the sequence as set forth in SEQ ID NO: 21, and (b) the second antigen-binding domain comprises a VH comprising the sequence as set forth in SEQ ID NO: 52, and a VL comprising the sequence as set forth in SEQ ID NO: 51.

4. The use according to any one of Claims 1 to 3, wherein the anti-HER2 biparatopic antibody comprises a heavy chain H1 comprising the sequence set forth in SEQ ID NO: 30, a

heavy chain H2 comprising the sequence set forth in SEQ ID NO: 50, and a light chain L1 comprising the sequence set forth in SEQ ID NO: 20.

5. The use according to any one of Claims 1 to 4, wherein the HER2-expressing cancer is a solid tumor.

6. The use according to any one of Claims 1 to 5, wherein the HER2-expressing cancer is breast cancer, biliary tract cancer, gastroesophageal adenocarcinoma (GEA), gastroesophageal junction cancer (GEJ), gastric cancer, esophageal cancer, endometrial cancer, ovarian cancer, cervical cancer, non-small cell lung cancer (NSCLC), anal cancer or colorectal cancer (CRC).

7. The use according to any one of Claims 1 to 5, wherein the HER2-expressing cancer is gastroesophageal adenocarcinoma (GEA).

8. The use according to any one of Claims 1 to 7, wherein the subject has received prior treatment with one or more of the anti-HER2-targeted therapies trastuzumab, pertuzumab, T-DM1 or Enhertu™ (fam-trastuzumab deruxtecan-nxki).

9. The use according to any one of Claims 1 to 7, wherein the subject has not received prior treatment with an anti-HER2 targeted therapy.

10. The use according to any one of Claims 1 to 9, wherein the subject has not received prior systemic treatment with a chemotherapeutic agent.

11. The use according to any one of Claims 1 to 10, wherein the cancer is metastatic.

12. The use according to any one of Claims 1 to 10, wherein the cancer is locally advanced.

13. The use according to any one of Claims 1 to 12, wherein the cancer is HER2 3+, HER2 2+/3+, HER2 2+ or HER2 1+ as measured by immunohistochemistry (IHC) and is gene amplified as measured by fluorescence in situ hybridization (FISH) or in situ hybridization (ISH).

14. The use according to any one of Claims 1 to 12, wherein the cancer is HER2 3+, HER2 2+/3+ or HER2 2+ or HER2 1+ as measured by immunohistochemistry (IHC) with or without HER2 gene amplification as measured by fluorescence in situ hybridization (FISH) or in situ hybridization (ISH).

15. The use according to any one of Claims 1 to 12, wherein the cancer is HER2 3+ as measured by IHC with or without HER2 gene amplification.

16. The use according to any one of Claims 1 to 12, wherein the cancer is HER2 2+ as measured by IHC with HER2 gene amplification, as measured by FISH or ISH.

17. The use according to any one of Claims 1 to 16, wherein the anti-HER2 biparatopic antibody is to be administered in combination with one or more chemotherapy regimens.

18. The use according to Claim 17, wherein the chemotherapy regimen comprises mFOLFOX6 (5-FU and leucovorin plus oxaliplatin), CAPOX (capecitabine plus oxaliplatin) or FP (fluorouracil [5-FU] plus cisplatin).

19. The use according to Claim 17, wherein the chemotherapy regimen comprises a taxane.

20. The use according to any one of Claims 1 to 19, wherein the anti-HER2 biparatopic antibody is to be administered in combination with a PD-1 inhibitor.

21. The use according to any one of Claims 1 to 20, wherein the anti-HER2 biparatopic antibody is to be administered in combination with another anti-HER2 agent.

22. The use according to Claim 20, wherein the PD-1 inhibitor is an anti-PD-1 antibody.

23. The use according to Claim 22, wherein the anti-PD-1 antibody is selected from tislelizumab, pembrolizumab, nivolumab or cemiplimab.

24. The use according to Claim 22, wherein the anti-PD-1 antibody is tislelizumab.

25. The use according to Claim 21, wherein the anti-HER2 agent is a tyrosine kinase inhibitor of the HER2 protein.