SUMMARY

[0010] In one aspect, the present disclosure provides a use of a composition comprising a therapeutically effective amount of tucatinib, or salt or solvate thereof, in the manufacture of a medicament for treating cancer in a subject, wherein: (a) the cancer has been determined to express a mutant form of HER2; or (b) the cancer expresses a mutant form of HER2. In another aspect, the present disclosure provides a use of a kit comprising tucatinib, or salt or solvate thereof in the manufacture of a medicament for treating cancer in a subject, wherein the cancer has been determined to express a mutant form of HER2, or the cancer expresses a mutant form of HER2.

[0010a] Provided herein is a method for treating cancer in a subject comprising administering a therapeutically effective amount of tucatinib, or salt or solvate thereof, to the subject, wherein the cancer has been determined to express a mutant form of HER2. Also provided herein is a method for treating cancer in a subject comprising administering a therapeutically effective amount of tucatinib, or salt or solvate thereof, to the subject, wherein the cancer expresses a mutant form of HER2. In some examples, the mutant form of HER2 is determined by DNA sequencing. In some examples, the mutant form of HER2 is determined by determining RNA sequencing. In some examples, the mutant form of HER2 is determined by nucleic acid sequencing. In some examples, the nucleic acid sequencing is next-generation sequencing (NGS). In some examples, the mutant form of HER2 is determined by polymerase chain reaction (PCR). In some examples, the mutant form of HER2 is determined by analyzing a sample obtained from the subject. In some examples, the sample obtained from the subject is a cell-free plasma sample. In some examples, the sample obtained from the subject is a tumor biopsy. In some examples, the cancer does not have HER2 amplification and the absence of HER2 amplification is determined by immunohistochemistry (IHC). In some examples, the cancer has a HER2 amplification score of 0 or 1+ and the HER2 amplification score is determined by immunohistochemistry (IHC). In some examples, the cancer has less than a 2 fold increase in HER2 protein levels. In some examples, the mutant form of HER2 comprises at least one amino acid substitution, insertion, or deletion compared to the amino acid sequence of SEQ ID NO:1. In some examples, the mutation in HER2 is an activating mutation. In some examples, the mutant form of HER2 comprises the amino acid substitution L755S. In some examples, the mutant form of HER2 comprises the amino acid substitution V777L. In some examples, the mutant form of HER2 comprises the amino acid substitution S310Y. In some examples, the mutant form of HER2 comprises a G776 YVMA insertion (G776 ins YVMA). In some examples, the cancer is

selected from the group consisting of gastric cancer, colorectal cancer, lung cancer, gall bladder cancer, and breast cancer. In some examples, the lung cancer is non-small cell lung cancer. In some examples, the breast cancer is a HER2 positive breast cancer. In some examples, the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 150 mg to about 650 mg. In some examples, the tucatinib, or salt or solvate thereof, is administered to

the subject at a dose of about 300 mg. In some examples, the tucatinib, or salt or solvate thereof, is administered once or twice per day. In some examples, the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 300 mg twice per day. In some examples, the tucatinib is administered to the subject orally. In some examples, the method further comprises administering one or more additional therapeutic agents to the subject to treat the cancer. In some examples, the one or more additional therapeutic agents is selected from the group consisting of capecitabine and an anti-HER2 antibody. In some examples, the one or more additional therapeutic agents is capecitabine. In some examples, the one or more additional therapeutic agents is trastuzumab. In some examples, the one or more additional therapeutic agents are capecitabine and trastuzumab. In some examples, the capecitabine is administered to the subject at a dose of about 500 mg/m^2 to about 1500 mg/m^2. In some examples, the capecitabine is administered to the subject at a dose of about 1000 mg/m^2. In some examples, the capecitabine is administered to the subject orally. In some examples, the capecitabine is administered to the subject twice per day. In some examples, the trastuzumab is administered to the subject at a dose of about 400 mg to about 800 mg. In some examples, the trastuzumab is administered to the subject at a dose of about 600 mg. In some examples, the trastuzumab is administered to the subject subcutaneously. In some examples, the trastuzumab is administered to the subject intraperitoneally. In some examples, the trastuzumab is administered to the subject at a dose of about 4 mg/kg to about 10 mg/kg. In some examples, the trastuzumab is administered to the subject at a dose of about 6 mg/kg. In some examples, the trastuzumab is administered to the subject at a dose of about 8 mg/kg. In some examples, the trastuzumab is administered to the subject at an initial dose of about 8 mg/kg followed by subsequent doses of about 6 mg/kg. In some examples, the trastuzumab is administered intravenously. In some examples, the trastuzumab is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, or once about every 4 weeks. In some examples, the trastuzumab is administered once about every 3 weeks. In some examples, the tucatinib, capecitabine and trastuzumab are administered to the subject on a 21 day treatment cycle. In some examples, the tucatinib is administered to the subject twice per day on each day of the 21 day treatment cycle. In some examples, the capecitabine is administered to the subject twice per day on each of days 1-14 of the 21 day treatment cycle. In some examples, the trastuzumab is

administered to the subject once per 21 day treatment cycle. In some examples, the dose of trastuzumab during the first 21 day treatment cycle is 8 mg/kg and the dose of trastuzumab during the subsequent 21 day treatment cycles is 6 mg/kg. In some examples, treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%. In some examples, treating the subject results in a TGI index of about 100%. In some examples, one or more therapeutic effects in the subject is improved after administration of tucatinib to the subject relative to a baseline. In some examples, the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival and overall survival. In some examples, the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of tucatinib to the subject. In some examples, the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%. In some examples, the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of tucatinib to the subject. In some examples, the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of tucatinib to the subject. In some examples, the duration of response to tucatinib is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months,

at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of tucatinib to the subject. In some examples, the subject is a human.

[0011] Also provided herein is the use of a therapeutically effective amount of tucatinib, or salt or solvate thereof, for the manufacture of a medicament for use according to any of the examples herein.

[0012] Also provided herein is tucatinib, or a salt or solvate thereof, for use according to any of the examples herein.

[0013] Also provided herein is a kit comprising tucatinib, or salt or solvate thereof, and instructions for using the kit according to any of the examples herein.

[0014] 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

[0015] 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.

[0016] FIG. 1 is a graph showing mean (± SEM) tumor volume over time of mice treated with vehicle, tucatinib, trastuzumab, or a combination of tucatinib and trastuzumab in the GL1208 gallbladder cancer xenograft model.

[0017] FIG. 2A is a graph showing mean (± SEM) tumor volume over time of mice treated with vehicle, tucatinib, trastuzumab, or a combination of tucatinib and trastuzumab in the CR3056 colorectal cancer xenograft model. FIG. 2B is a graph showing tucatinib mediated inhibition of HER2 V777L kinase activity.

CLAIMS

What is claimed is:

1. Use of a composition comprising a therapeutically effective amount of tucatinib, or salt or solvate thereof, in the manufacture of a medicament for treating cancer in a subject, wherein:

(a) the cancer has been determined to express a mutant form of HER2; or

(b) the cancer expresses a mutant form of HER2.

2. The use of claim 1, wherein the mutant form of HER2 is determined by nucleic acid sequencing.

3. The use of claim 2, wherein the nucleic acid sequencing is:

(a) DNA sequencing;

(b) RNA sequencing;

(c) polymerase chain reaction (PCR); and/or

(d) next-generation sequencing (NGS).

4. The use of any one of claims 1-3, wherein the mutant form of HER2 is determined by analyzing a sample obtained from the subject.

5. The use of claim 4, wherein the sample obtained from the subject is a cell-free plasma sample or a tumor biopsy.

6. The use of any one of claims 1-5, wherein the cancer does not have HER2 amplification, and wherein the absence of HER2 amplification is determined by immunohistochemistry (IHC).

7. The use of any one of claims 1-5, wherein the cancer has a HER2 amplification score of 0 or 1+, and wherein the HER2 amplification score is determined by immunohistochemistry (IHC).

8. The use of any one of claims 1-6, wherein the cancer has less than a 2 fold increase in HER2 protein levels.

9. The use of any one of claims 1-8, wherein the mutant form of HER2 comprises at least one amino acid substitution, insertion, or deletion compared to the amino acid sequence of SEQ ID NO:1.

10. The use of any one of claims 1-9, wherein the mutation in HER2 is an activating mutation.

11. The use of any one of claims 1-10, wherein the mutant form of HER2 comprises:

(a) the amino acid substitution L755S

(b) the amino acid substitution V777L;

(c) the amino acid substitution S310Y; and/or

(d) a G776 YVMA insertion (G776 ins YVMA).

12. The use of any one of claims 1-11, wherein the cancer is selected from the group consisting of gastric cancer, colorectal cancer, lung cancer, optionally wherein the lung cancer is non-small cell lung cancer, gall bladder cancer, and breast cancer, optionally wherein the breast cancer is a HER2 positive breast cancer.

13. The use of any one of claims 1-12, wherein:

(a) the therapeutically effective amount of tucatinib, or salt or solvate thereof, to be administered to the subject is at a dose of 150 mg to 650 mg;

(b) the therapeutically effective amount of tucatinib to be administered to the subject is at a dose of about 300 mg;

(c) the tucatinib is to be administered to the subject once or twice per day, optionally wherein the tucatinib is to be administered to the subject at a dose of about 300 mg twice per day;

(d) the tucatinib is manufactured to be administered orally.

14. The use of any one of claims 1-13, further comprising that one or more additional therapeutic agents are to be administered to the subject to treat the cancer; optionally wherein the one or more additional therapeutic agents is selected from the group consisting of capecitabine and an anti-HER2 antibody; optionally wherein the one or more additional therapeutic agents is capecitabine and/or trastuzumab.

15. The use of claim 14, wherein the one or more additional therapeutic agents comprise capecitabine, wherein the capecitabine is to be administered to the subject at a dose of 500 mg/m2 to 1500 mg/m2; optionally wherein the capecitabine is to be administered to the subject at a dose of about 1000 mg/m2; optionally wherein the capecitabine is to be administered to the subject orally; optionally wherein the capecitabine is to be administered to the subject twice per day.

16. The use of claim 14, wherein the one or more additional therapeutic agents comprise trastuzumab, wherein:

(a) the trastuzumab is to be administered to the subject at a dose of 400 mg to 800 mg, optionally wherein:

(i) the trastuzumab is to be administered to the subject at a dose of about 600 mg, and/or (ii) the trastuzumab is to be administered to the subject subcutaneously;

(b) the trastuzumab is to be administered to the subject intraperitoneally; or

(c) the trastuzumab is to be administered to the subject at a dose of 4 mg/kg to 10 mg/kg, optionally wherein:

(i) the trastuzumab is to be administered to the subject at a dose of about 6 mg/kg,

(ii) the trastuzumab is to be administered to the subject at a dose of about 6 mg/kg,

(iii) the trastuzumab is to be administered to the subject at an initial dose of about 8 mg/kg followed by subsequent doses of about 6 mg/kg, and/or

(iv) the trastuzumab is to be administered intravenously.

17. The use of claim 16, wherein the trastuzumab is to be administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, or once about every 4 weeks; optionally wherein the trastuzumab is to be administered once about every 3 weeks.

18. The use of claim 17, wherein the tucatinib, capecitabine and trastuzumab are to be administered to the subject on a 21 day treatment cycle; wherein the tucatinib is to be administered to the subject twice per day on each day of the 21 day treatment cycle; optionally wherein the capecitabine is to be administered to the subject twice per day on each of days 1-14 of the 21 day treatment cycle; optionally wherein the trastuzumab is to be administered to the subject once per 21 day treatment cycle; optionally wherein the dose of trastuzumab during the first 21 day treatment

cycle is 8 mg/kg and the dose of trastuzumab during the subsequent 21 day treatment cycles is 6 mg/kg.

19. The use of any one of claims 1-18, wherein treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%; optionally wherein treating the subject results in a TGI index of about 100%.

20. The use of any one of claims 1-19, wherein one or more therapeutic effects in the subject is improved after administration of tucatinib to the subject relative to a baseline; optionally wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival and overall survival.

21. The use of any one of claims 1-20, wherein:

(a) the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of tucatinib to the subject;

(b) the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%;

(c) the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of tucatinib to the subject;

(d) the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two

years, at least about three years, at least about four years, or at least about five years after administration of tucatinib to the subject; and/or

(e) the duration of response to tucatinib is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of tucatinib to the subject.

22. The use of any one of claims 1-21, wherein the subject is a human.

23. Use of a kit comprising tucatinib, or salt or solvate thereof in the manufacture of a medicament for treating cancer in a subject, wherein the cancer has been determined to express a mutant form of HER2, or the cancer expresses a mutant form of HER2.