

in vitro, and in cellular signaling assays is >1000-fold more selective for HER2 compared to the closely related kinase EGFR. The selectivity of tucatinib for HER2 reduces the potential for EGFR-related toxicities that can be seen with dual HER2/EGFR inhibitors. Tucatinib inhibits the HER2-driven mitogen-activated protein and PI3 kinase signaling pathways, resulting in inhibition of tumor cell proliferation, survival, and metastasis.

[0008] Tucatinib, combined with trastuzumab and capecitabine, is approved for use in previously treated patients with advanced unresectable or metastatic HER2+ breast cancer in Australia, Canada, Singapore, Switzerland, and the US.

[0009] Trastuzumab, a humanized anti-HER2 antibody that binds to the HER2 extracellular domain, is approved for use in the treatment of HER2+ breast cancer and remains the backbone of treatment in the perioperative and metastatic setting, usually in combination with a taxane. Pertuzumab is another approved anti-HER2 monoclonal antibody, which binds to the HER2 receptor at a site different from trastuzumab.

[0010] All references cited herein, including patent applications, patent publications, and scientific literature, are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

[0011] In one aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, and at least one anti-HER2 antibody in the manufacture of a medicament for combination therapy to treat a solid tumor in a subject, wherein the solid tumor has one or more HER2 alterations. In another aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a first medicament and use of at least one anti-HER2 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a solid tumor in a subject, wherein the solid tumor has one or more HER2 alterations. In yet another aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a subject, wherein said medicament is to be administered in combination with at least one anti-HER2 antibody, wherein the solid tumor has one or more HER2 alterations. In a further aspect, the present disclosure provides a use of at

least one anti-HER2 antibody in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a subject, wherein said medicament is to be administered in combination with tucatinib, or a salt or solvate thereof, wherein the solid tumor has one or more HER2 alterations.

[0011a] In a further aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for increasing the overall amount of HER2 in a solid tumor, wherein the administration of the tucatinib, or salt or solvate thereof, to a subject increases the overall amount of HER2 in the solid tumor. In a further aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for increasing the amount of plasma membrane-bound HER2 in a solid tumor, wherein the administration of the tucatinib, or salt or solvate thereof, to a subject increases the amount of plasma membrane-bound HER2 in the solid tumor. In a further aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for increasing dwell time of HER2 at the cell surface of a solid tumor, wherein the administration of the tucatinib, or salt or solvate thereof, to a subject increases the dwell time of HER2 at the cell surface. In a further aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for increasing internalization of plasma membrane-bound HER2 in a solid tumor, wherein the administration of the tucatinib, or salt or solvate thereof, to a subject increases the internalization of plasma membrane-bound HER2. In a further aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for increasing lysosomal degradation of HER2 in a solid tumor, wherein the administration of the tucatinib, or salt or solvate thereof, to subject increases the lysosomal degradation of HER2. In yet another aspect, the present disclosure provides a kit comprising: (a) tucatinib, or salt or solvate thereof; (b) at least one anti-HER2 antibody; and (c) instructions for using the kit to treat a solid tumor in a subject.

[0011b] Provided herein is a method for treating a solid tumor in a subject comprising administering a combination of tucatinib, or salt or solvate thereof, and at least one anti-HER2 antibody to the subject, wherein the solid tumor has one or more HER2 alterations. In some embodimentexamples, the subject exhibits progression free survival (PFS) of at least 1 month after administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody. In some embodimentexamples, the subject exhibits an overall survival (OS) of at least 2 months

after administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody. In some embodiment examples, the subject exhibits a greater than 10% reduction in the risk of disease progression as compared to a subject administered the at least one anti-HER2 antibody alone. In some embodiment examples, the subject exhibits a greater than 25% reduction in the risk of disease progression as compared to a subject administered the at least one anti-HER2 antibody alone. In some embodiment examples, the subject exhibits a greater than 30% reduction in the

risk of disease progression as compared to a subject administered the at least one anti-HER2 antibody alone. In some [embodimentexamples](#), the subject exhibits a greater than 10% reduction in the risk of death as compared to a subject administered the at least one anti-HER2 antibody alone. In some [embodimentexamples](#), the subject exhibits a greater than 25% reduction in the risk of death as compared to a subject administered the at least one anti-HER2 antibody alone. In some [embodimentexamples](#), the subject exhibits a greater than 30% reduction in the risk of death as compared to a subject administered the at least one anti-HER2 antibody alone. In some [embodimentexamples](#), following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for nine months the subject has an estimated PFS rate of greater than 20%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 30%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 40%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 45%. In some [embodimentexamples](#), following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for twelve months the subject has an estimated PFS rate of greater than 15%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 20%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 30%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 40%. In some [embodimentexamples](#), following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for fifteen months the subject has an estimated PFS rate of greater than 15%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 20%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 25%. In some [embodimentexamples](#), the subject has an estimated PFS rate of greater than 30%. In some [embodimentexamples](#), following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for twenty-four months the subject has an estimated OS rate of greater than 25%. In some [embodimentexamples](#), the subject has an estimated OS rate of greater than 35%. In some [embodimentexamples](#), the subject has an estimated OS rate of greater than 40%. In some [embodimentexamples](#), following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for thirty months the subject has an estimated OS rate of greater than 20%. In some [embodimentexamples](#), the subject has an estimated OS rate of greater than 25%. In some [embodimentexamples](#), the subject has an estimated OS rate of greater than 30%. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, and at least one anti-HER2 antibody are administered to the subject on a 21-day treatment cycle. In some

embodimentexamples, the at least one anti-HER2 antibody is administered to the subject on day 1 of the 21-day treatment cycle. In some embodimentexamples, the at least one anti-HER2 antibody is administered once about every 3 weeks. In some embodimentexamples, the tucatinib, or salt or solvate thereof, is administered to the subject twice per day. In some embodimentexamples, the one or more HER2 alterations is a HER2 mutation, wherein the HER2 mutation comprises at least one amino acid substitution, insertion, or deletion compared to the amino acid sequence of SEQ ID NO:1. In some embodimentexamples, the HER2 mutation is an activating mutation. In some embodimentexamples, the HER2 mutation is a mutation in the extracellular domain, the kinase domain, or the transmembrane/juxtamembrane domain, or any combination thereof. In some embodimentexamples, the HER2 mutation is a mutation in the extracellular domain selected from the group consisting of G309A, G309E, S310F, S310Y, C311R, C311S, and C334S. In some embodimentexamples, the HER2 mutation is a mutation in the kinase domain at an amino acid residue selected from the group consisting of Y772, G776, G778, and T798. In some embodimentexamples, the HER2 mutation is a G776 YVMA insertion. In some embodimentexamples, the HER2 mutation is a mutation in the kinase domain selected from the group consisting of T733I, L755P, L755S, I767M, L768S, D769N, D769Y, D769H, V777L, V777M, L841V, V842I, N857S, T862A, L869R, H878Y, and R896C. In some embodimentexamples, the HER2 mutation is a mutation in the kinase domain at an amino acid residue V697. In some embodimentexamples, the HER2 mutation is a mutation in the transmembrane/juxtamembrane domain selected from the group consisting of S653C, I655V, V659E, G660D, and R678Q. In some embodimentexamples, the HER2 mutation is determined by using next generation sequencing (NGS). In some embodimentexamples, the one or more HER2 alterations is HER2 overexpression/amplification. In some embodimentexamples, the HER2 overexpression is 3+ overexpression as determined by immunohistochemistry (IHC). In some embodimentexamples, the HER2 amplification is determined by an *in situ* hybridization assay. In some embodimentexamples, the *in situ* hybridization assay is fluorescence *in situ* hybridization (FISH) assay. In some embodimentexamples, the *in situ* hybridization assay is chromogenic *in situ* hybridization. In some embodimentexamples, the HER2 amplification is determined in tissue by NGS. In some embodimentexamples, the HER2 amplification is determined in circulating tumor DNA (ctDNA) by a blood-based NGS assay. In some embodimentexamples, the solid tumor is a HER2+ solid tumor. In some embodimentexamples, the solid tumor is a metastatic solid tumor. In some embodimentexamples, the solid tumor is locally-advanced. In some embodimentexamples, the solid tumor is unresectable. In some embodimentexamples, the solid

tumor is selected from the group consisting of cervical cancer, uterine cancer, gallbladder cancer, cholangiocarcinoma, urothelial cancer, lung cancer, breast cancer, gastroesophageal cancer, and colorectal cancer. In some [embodimentexamples](#), the solid tumor is gallbladder cancer and the subject has completed at least one prior line of treatment for the gallbladder cancer. In some [embodimentexamples](#), the prior line of treatment is selected from the group consisting of chemotherapy, endocrine therapy, and targeted therapy. In some [embodimentexamples](#), the solid tumor is cholangiocarcinoma and the subject has completed at least one prior line of treatment for the cholangiocarcinoma. In some [embodimentexamples](#), the prior line of treatment is selected from the group consisting of chemotherapy, endocrine therapy, and targeted therapy. In some [embodimentexamples](#), the lung cancer is non-small cell lung cancer (NSCLC). In some [embodimentexamples](#), the NSCLC is non-squamous NSCLC. In some [embodimentexamples](#), the subject has relapsed from standard of care treatment. In some [embodimentexamples](#), the subject is refractory to standard of care treatment. In some [embodimentexamples](#), no standard of care treatment is available for the subject. In some [embodimentexamples](#), the solid tumor is breast cancer. In some [embodimentexamples](#), the subject has completed at least one prior line of treatment for the breast cancer. In some [embodimentexamples](#), the prior line of treatment is selected from the group consisting of chemotherapy, endocrine therapy, and targeted therapy. In some [embodimentexamples](#), the breast cancer is hormone receptor positive (HR+) breast cancer. In some [embodimentexamples](#), the breast cancer is a metastasized breast cancer. In some [embodimentexamples](#), the subject is administered fulvestrant in combination with the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody. In some [embodimentexamples](#), the fulvestrant is administered at a dose of 500 mg. In some [embodimentexamples](#), the route of administration of the fulvestrant is administered intramuscular (IM). In some [embodimentexamples](#), the fulvestrant is administered on day 1 of the first 21-day treatment cycle. In some [embodimentexamples](#), the fulvestrant is administered once about every 4 weeks. In some [embodimentexamples](#), the fulvestrant is further administered on day 15 of the first 21-day treatment cycle. In some [embodimentexamples](#), 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 [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 300 mg. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject orally. In some [embodimentexamples](#), the at least one anti-HER2 antibody is administered to the subject at a dose of about 4 mg/kg to about 10 mg/kg. In some [embodimentexamples](#), the at least one anti-HER2 antibody is administered to the subject at a dose of about 6 mg/kg of the subject's body weight.

In some [embodimentexamples](#), the at least one anti-HER2 antibody is administered to the subject at a dose of about 8 mg/kg of the subject's body weight. In some [embodimentexamples](#), the at least one anti-HER2 antibody is administered to the subject at a dose of about an initial dose of about 8 mg/kg followed by subsequent doses of about 6 mg/kg. In some [embodimentexamples](#), the dose of the at least one anti-HER2 antibody administered during the first 21-day treatment cycle is 8 mg/kg of the subject's body weight and the dose administered during the subsequent 21-day treatment cycles is 6 mg/kg of the subject's bodyweight. In some [embodimentexample](#)s, the at least one anti-HER2 antibody is administered intravenously. In some [embodimentexamples](#), the at least one anti-HER2 antibody comprises one anti-HER2 antibody. In some [embodimentexamples](#), the at least one anti-HER2 antibody is no more than one anti-HER2 antibody. In some [embodimentexamples](#), the at least one anti-HER2 antibody is trastuzumab, or a biosimilar thereof. In some [embodimentexamples](#), the at least one anti-HER2 antibody is trastuzumab. In some [embodimentexamples](#), the at least one anti-HER2 antibody comprises a first anti-HER2 antibody and a second anti-HER2 antibody. In some [embodimentexamples](#), the first anti-HER2 antibody is administered to the subject at a dose of about 4 mg/kg to about 10 mg/kg. In some [embodimentexamples](#), the first anti-HER2 antibody is administered to the subject at a dose of about 6 mg/kg of the subject's body weight. In some [embodimentexamples](#), the first anti-HER2 antibody is administered at a dose of about 200 mg to about 1,000 mg. In some [embodimentexamples](#), the first anti-HER2 antibody is administered at a dose of about 600 mg. In some [embodimentexamples](#), the second anti-HER2 antibody is administered to the subject at a dose of about 200 mg to about 1,000 mg. In some [embodimentexamples](#), the second anti-HER2 antibody is administered at a dose of about 420 mg. In some [embodimentexamples](#), the second anti-HER2 antibody is administered at a dose of about 600 mg. In some [embodimentexamples](#), the first anti-HER2 antibody is administered at a dose of about 6 mg/kg and the second anti-HER2 antibody is administered at a dose of about 420 mg. In some [embodimentexamples](#), the first anti-HER2 antibody is administered intravenously. In some [embodimentexamples](#), the first anti-HER2 antibody is administered subcutaneously. In some [embodimentexamples](#), the second anti-HER2 antibody is administered intravenously. In some [embodimentexamples](#), the second anti-HER2 antibody is administered subcutaneously. In some [embodimentexamples](#), the first anti-HER2 antibody is administered at a dose of 6 mg/kg intravenously or at a dose of about 600 mg subcutaneously; and wherein the second anti-HER2 antibody is administered at a dose of about 420 mg intravenously. In some [embodimentexamples](#), the first anti-HER2 antibody and the second anti-HER2 antibody are administered in a pharmaceutical composition

comprising about 600 mg of the first anti-HER2 antibody and 600 mg of the second anti-HER2 antibody; wherein the pharmaceutical composition is administered subcutaneously. In some [embodimentexamples](#), the pharmaceutical composition further comprises hyaluronidase. In some [embodimentexamples](#), the pharmaceutical composition comprises about 20,000 units hyaluronidase. In some [embodimentexamples](#), the first anti-HER2 antibody is trastuzumab, or a biosimilar thereof. In some [embodimentexamples](#), the second anti-HER2 antibody is pertuzumab, or a biosimilar thereof. In some [embodimentexamples](#), the first anti-HER2 antibody is administered about once every 3 weeks. In some [embodimentexamples](#), the second anti-HER2 antibody is administered about once every 3 weeks. In some [embodimentexamples](#), treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%. In some [embodimentexamples](#), treating the subject results in a TGI index of about 100%. In some [embodimentexamples](#), one or more therapeutic effects in the subject is improved after administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody to the subject relative to a baseline. In some [embodimentexamples](#), the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the solid tumor, objective response rate, duration of response, time to response, progression free survival and overall survival. In some [embodimentexamples](#), the size of a tumor derived from the solid tumor 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 solid tumor before administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody. In some [embodimentexamples](#), 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 [embodimentexamples](#), the subject exhibits progression-free survival of 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 the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody. In some [embodimentexamples](#), the subject exhibits overall survival of 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 the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody. In some embodimentexamples, 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 the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody. In some embodimentexamples, the administration of the tucatinib, or salt or solvate thereof, increases the overall amount of HER2 in the solid tumor. In some embodimentexamples, the overall amount of HER2 in the solid tumor is determined by western blot analysis. In some embodimentexamples, the administration of the tucatinib, or salt or solvate thereof, increases the amount of plasma membrane-bound HER2 in the solid tumor. In some embodimentexamples, the amount of plasma membrane-bound HER2 in the solid tumor is determined by quantitative fluorescence activated cell sorting (qFACS). In some embodimentexamples, the administration of the tucatinib, or salt or solvate thereof, increases the dwell time of HER2 at the cell surface. In some embodimentexamples, the administration of the tucatinib, or salt or solvate thereof, increases the internalization of plasma membrane-bound HER2. In some embodimentexamples, the administration of the tucatinib, or salt or solvate thereof, increases the lysosomal degradation of HER2. In some embodimentexamples, the subject is a human.

[0012] Also provided herein is a method of increasing the overall amount of HER2 in a solid tumor comprising administering tucatinib, or salt or solvate thereof to a subject, wherein the administration of the tucatinib, or salt or solvate thereof, increases the overall amount of HER2 in the solid tumor. In some embodimentexamples, the overall amount of HER2 in the solid tumor is determined by Western blot analysis.

[0013] Also provided herein is a method of increasing the amount of plasma membrane-bound HER2 in a solid tumor comprising administering tucatinib, or salt or solvate thereof to a subject, wherein the administration of the tucatinib, or salt or solvate thereof, increases the

amount of plasma membrane-bound HER2 in the solid tumor. In some [embodimentexamples](#), the amount of plasma membrane-bound HER2 in the solid tumor is determined by quantitative fluorescence activated cell sorting (qFACS).

[0014] Also provided herein is a method of increasing dwell time of HER2 at the cell surface of a solid tumor comprising administering tucatinib, or salt or solvate thereof to a subject, wherein the administration of the tucatinib, or salt or solvate thereof, increases the dwell time of HER2 at the cell surface.

[0015] Also provided herein is a method of increasing internalization of plasma membrane-bound HER2 in a solid tumor comprising administering tucatinib, or salt or solvate thereof to a subject, wherein the administration of the tucatinib, or salt or solvate thereof, increases the internalization of plasma membrane-bound HER2.

[0016] Also provided herein is a method of increasing lysosomal degradation of HER2 in a solid tumor comprising administering tucatinib, or salt or solvate thereof to a subject, wherein the administration of the tucatinib, or salt or solvate thereof, increases the lysosomal degradation of HER2.

[0017] Also provided herein is a kit comprising tucatinib, or salt or solvate thereof, at least one anti-HER2 antibody, and instructions for using the kit according to any of the [embodimentexamples](#) herein. In some [embodimentexamples](#), the at least one anti-HER2 antibody comprises trastuzumab. In some [embodimentexamples](#), the at least one anti-HER2 antibody comprises pertuzumab.

[0018] It is to be understood that one, some, or all of the properties of the various [embodimentexamples](#) described herein may be combined to form other [embodimentexamples](#) of the present [inventiondisclosure](#). These and other [aspectexamples](#) of the [inventiondisclosure](#) will become apparent to one of skill in the art. These and other [embodimentexamples](#) of the [inventiondisclosure](#) are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIGs. 1A-1H are a series of graphs showing that treatment with tucatinib increased overall and plasma membrane-bound HER2 levels in BT-474, SK-BR-3, HCC-1419, and UACC-893 cell lines after treatment with tucatinib at either 30nM or 100nM doses for the duration of 24 hours and 48 hours.

CLAIMS

What is claimed is:

1. Use of tucatinib, or a salt or solvate thereof, and at least one anti-HER2 antibody in the manufacture of a medicament ~~A method for combination therapy to treating~~ a solid tumor in a subject ~~comprising administering a combination of tucatinib, or salt or solvate thereof, and at least one anti-HER2 antibody to the subject,~~ wherein the solid tumor has one or more HER2 alterations.
2. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a first medicament and use of at least one anti-HER2 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a solid tumor in a subject, wherein the solid tumor has one or more HER2 alterations.
3. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a subject, wherein said medicament is to be administered in combination with at least one anti-HER2 antibody, wherein the solid tumor has one or more HER2 alterations.
4. Use of at least one anti-HER2 antibody in the manufacture of a medicament for use in combinatorial therapy for treating a solid tumor in a subject, wherein said medicament is to be administered in combination with tucatinib, or a salt or solvate thereof, wherein the solid tumor has one or more HER2 alterations.
25. The use of any one of claims 1-4 ~~method of claim 1,~~ wherein:
 - (a) the subject exhibits progression free survival (PFS) of at least 1 month after administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody;
 - (b)

~~3. The method of claim 1 or claim 2, wherein~~ the subject exhibits an overall survival (OS) of at least 2 months after administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody;

(c)

~~4. The method of any one of claims 1-3, wherein~~ the subject exhibits a greater than 10% reduction in the risk of disease progression as compared to a subject to be administered the at least one anti-HER2 antibody alone;

~~5. The method of claim 4, wherein the subject exhibits a greater than 25% reduction in the risk of disease progression as compared to a subject administered the at least one anti-HER2 antibody alone.~~

~~6. The method of claim 4, wherein the subject exhibits a greater than 30% reduction in the risk of disease progression as compared to a subject administered the at least one anti-HER2 antibody alone.~~(d)

~~7. The method of any one of claims 1-6, wherein~~ the subject exhibits a greater than 10% reduction in the risk of death as compared to a subject to be administered the at least one anti-HER2 antibody alone;

~~8. The method of claim 7, wherein the subject exhibits a greater than 25% reduction in the risk of death as compared to a subject administered the at least one anti-HER2 antibody alone.~~

~~9. The method of claim 7, wherein the subject exhibits a greater than 30% reduction in the risk of death as compared to a subject administered the at least one anti-HER2 antibody alone.~~(e)

~~10. The method of any one of claims 1-9, wherein~~ following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for nine months the subject has an estimated PFS rate of greater than 20%;

~~(f)-~~

~~11. The method of claim 10, wherein the subject has an estimated PFS rate of greater than 30%.~~

~~12. The method of claim 10, wherein the subject has an estimated PFS rate of greater than 40%.~~

~~13. The method of claim 10, wherein the subject has an estimated PFS rate of greater than 45%.~~

~~14. The method of any one of claims 1-9, wherein~~ following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for twelve months the subject has an estimated PFS rate of greater than 15%;

~~(g)~~

~~15. The method of claim 14, wherein the subject has an estimated PFS rate of greater than 20%.~~

~~16. The method of claim 14, wherein the subject has an estimated PFS rate of greater than 30%.~~

~~17. The method of claim 14, wherein the subject has an estimated PFS rate of greater than 40%.~~

~~18. The method of any one of claims 1-9, wherein~~ following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for fifteen months the subject has an estimated PFS rate of greater than 15%;

(h)

~~19. The method of claim 18, wherein the subject has an estimated PFS rate of greater than 20%.~~

~~20. The method of claim 18, wherein the subject has an estimated PFS rate of greater than 25%.~~

~~21. The method of claim 18, wherein the subject has an estimated PFS rate of greater than 30%.~~

~~22. The method of any one of claims 1-21, wherein~~ following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for twenty-four months the subject has an estimated OS rate of greater than 25%; and/or-

(i)

~~23. The method of claim 22, wherein the subject has an estimated OS rate of greater than 35%.~~

~~24. The method of claim 22, wherein the subject has an estimated OS rate of greater than 40%.~~

~~25. The method of any one of claims 1-21, wherein~~ following administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody, for thirty months the subject has an estimated OS rate of greater than 20%.

~~26. The method of claim 25, wherein the subject has an estimated OS rate of greater than 25%.~~

~~27. The method of claim 25, wherein the subject has an estimated OS rate of greater than 30%.~~

~~286~~. The ~~use~~method of any one of claims 1-~~527~~, wherein the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody are to be administered to the subject on a 21-day treatment cycle, optionally wherein:-

_____ (a)

~~29~~. ~~The method of claim 28, wherein~~ the at least one anti-HER2 antibody is to be administered to the subject on day 1 of the 21-day treatment cycle;

_____ (b);

~~30~~. ~~The method of any one of claims 1-29, wherein~~ the at least one anti-HER2 antibody is to be administered once about every 3 weeks;

_____ (c)

~~31~~. ~~The method of any one of claims 1-30, wherein~~ the tucatinib, or salt or solvate thereof, is to be administered to the subject twice per day.

~~327~~. The ~~method~~use of any one of claims 1-~~346~~, wherein the one or more HER2 alterations is a HER2 mutation, wherein the HER2 mutation comprises at least one amino acid substitution, insertion, or deletion compared to the amino acid sequence of SEQ ID NO:1.

~~338~~. The ~~method~~use of claim ~~327~~, wherein the HER2 mutation is an activating mutation.

~~349~~. The ~~method~~use of claim ~~327~~ or claim ~~338~~, wherein the HER2 mutation is a mutation in the extracellular domain, the kinase domain, or the transmembrane/juxtamembrane domain, or any combination thereof.

~~3510~~. The ~~method~~use of claim ~~349~~, wherein:

(a) the HER2 mutation is a mutation in the extracellular domain selected from the group consisting of G309A, G309E, S310F, S310Y, C311R, C311S, and C334S;

(b);

~~36. The method of claim 34, wherein~~ the HER2 mutation is a mutation in the kinase domain at an amino acid residue selected from the group consisting of Y772, G776, G778, and T798;

(c):-

~~37. The method of claim 34, wherein~~ the HER2 mutation is a G776 YVMA insertion;

(d):-

~~38. The method of claim 34, wherein~~ the HER2 mutation is a mutation in the kinase domain selected from the group consisting of T733I, L755P, L755S, I767M, L768S, D769N, D769Y, D769H, V777L, V777M, L841V, V842I, N857S, T862A, L869R, H878Y, and R896C;

(e):-

~~39. The method of claim 34, wherein~~ the HER2 mutation is a mutation in the kinase domain at an amino acid residue V697; or

(f):-

~~40. The method of claim 34, wherein~~ the HER2 mutation is a mutation in the transmembrane/juxtamembrane domain selected from the group consisting of S653C, I655V, V659E, G660D, and R678Q.

4111. The ~~use method~~ of any one of claims ~~327-4010~~, wherein the HER2 mutation is determined by using next generation sequencing (NGS).

4212. The ~~method use~~ of any one of claims 1-~~316~~, wherein the one or more HER2 alterations is HER2 overexpression/amplification.

4313. The ~~method use~~ of claim 4212, wherein:

(a) the HER2 overexpression is 3+ overexpression as determined by immunohistochemistry (IHC);

(b)

~~44. The method of claim 42, wherein~~ the HER2 amplification is determined by an *in situ* hybridization assay, optionally wherein -

~~45. The method of claim 44, wherein~~(i) the *in situ* hybridization assay is fluorescence *in situ* hybridization (FISH) assay-, or (ii)

~~46. The method of claim 44, wherein~~ the *in situ* hybridization assay is chromogenic *in situ* hybridization;

(c) -

~~47. The method of claim 42, wherein~~ the HER2 amplification is determined in tissue by NGS-; or

(d)

~~48. The method of claim 42, wherein~~ the HER2 amplification is determined in circulating tumor DNA (ctDNA) by a blood-based NGS assay.

~~49~~14. The ~~method~~use of any one of claims 1-~~48~~13, wherein:

(a) the solid tumor is a HER2+ solid tumor-;

(b)

~~50. The method of any one of claims 1-49, wherein~~ the solid tumor is a metastatic solid tumor-;

(c)

~~51. The method of any one of claims 1-50, wherein~~ the solid tumor is locally-advanced-; and/or

(d)

~~52. The method of any one of claims 1-51, wherein~~ the solid tumor is unresetable.

15.

~~53.~~ The ~~method use~~ of any one of claims 1-~~52~~14, wherein the solid tumor is selected from the group consisting of cervical cancer, uterine cancer, gallbladder cancer, cholangiocarcinoma, urothelial cancer, lung cancer, breast cancer, gastroesophageal cancer, and colorectal cancer.

~~54~~16. The ~~method use~~ of claim ~~53~~15, wherein:

(a) the solid tumor is gallbladder cancer and the subject has completed at least one prior line of treatment for the gallbladder cancer, optionally :

~~55. The method of claim 54,~~ wherein the prior line of treatment is selected from the group consisting of chemotherapy, endocrine therapy, and targeted therapy~~;~~:

(b)

~~56. The method of claim 53, wherein~~ the solid tumor is cholangiocarcinoma and the subject has completed at least one prior line of treatment for the cholangiocarcinoma, optionally :

~~57. The method of claim 56,~~ wherein the prior line of treatment is selected from the group consisting of chemotherapy, endocrine therapy, and targeted therapy~~;~~:

(c) the solid tumor is lung cancer that

~~58. The method of claim 53, wherein the lung cancer~~ is non-small cell lung cancer (NSCLC), optionally wherein :

~~59. The method of claim 58, wherein~~ the NSCLC is non-squamous NSCLC.

~~60. The method of claim 59, wherein the subject has relapsed from standard of care treatment.~~

~~61. The method of claim 59, wherein the subject is refractory to standard of care treatment.~~

~~62. The method of claim 59, wherein no standard of care treatment is available for the subject.~~

~~63~~17. The ~~method~~use of claim ~~53~~15, wherein the solid tumor is breast cancer, optionally wherein :

~~64. The method of claim 63, wherein the subject has completed at least one prior line of treatment for the breast cancer.~~

~~65. The method of claim 64, wherein the prior line of treatment is selected from the group consisting of chemotherapy, endocrine therapy, and targeted therapy.~~

~~66. The method of any one of claims 63-65, wherein~~ the breast cancer is hormone receptor positive (HR+) breast cancer, further optionally :

~~67. The method of any one of claims 63-66,~~ wherein the breast cancer is a metastasized breast cancer.

~~68~~18. The ~~method~~use of claim ~~66 or claim 67~~17, wherein the subject is to be administered fulvestrant in combination with the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody.

~~69~~19. The ~~use~~method of claim ~~68~~18, wherein:

(a) the fluvestrant is to be administered at a dose of 500 mg;_i:

(b)

~~70. The method of claim 68 or claim 69, wherein~~ the route of administration of the fluvestrant is to be administered intramuscular (IM);

(c);

~~71. The method of any one of claims 68-70, wherein~~ the fluvestrant is to be administered on day 1 of the first 21-day treatment cycle, optionally:-

~~72. The method of claim 71,~~ wherein the fluvestrant is to be administered once about every 4 week, optionally s:-

~~73. The method of claim 71 or claim 72,~~ wherein the fluvestrant is to be further administered on day 15 of the first 21-day treatment cycle.

~~74~~20. The ~~method~~use of any one of claims 1-~~73~~19, wherein:

(a) the tucatinib, or salt or solvate thereof, is to be administered to the subject at a dose of ~~about~~ 150 mg to ~~about~~ 650 mg, optionally:-

~~75. The method of claim 74,~~ wherein the tucatinib, or salt or solvate thereof, is to be administered to the subject at a dose of about 300 mg; and/or

(b):-

~~76. The method of any one of claims 1-75, wherein~~ the tucatinib, or salt or solvate thereof, is to be administered to the subject orally.

~~77~~21. The ~~method~~use of any one of claims 1-~~76~~20, wherein:

(a) the at least one anti-HER2 antibody is to be administered to the subject at a dose of ~~about~~ 4 mg/kg to ~~about~~ 10 mg/kg, optionally:-

~~78. The method of claim 77,~~ wherein the at least one anti-HER2 antibody is to be administered to the subject at a dose of about 6 mg/kg of the subject's body weight; or

~~79. The method of claim 78, wherein the at least one anti-HER2 antibody is administered to the subject~~ at a dose of about 8 mg/kg of the subject's body weight;:-

(b)

~~80. The method of claim 77, wherein~~ the at least one anti-HER2 antibody is to be administered to the subject at a dose of about an initial dose of about 8 mg/kg followed by subsequent doses of about 6 mg/kg;

(c)

~~81. The method of claim 77, wherein~~ the dose of the at least one anti-HER2 antibody to be administered during the first 21-day treatment cycle is 8 mg/kg of the subject's body weight and the dose to be administered during the subsequent 21-day treatment cycles is 6 mg/kg of the subject's bodyweight; ~~and/or~~

(d)

~~82. The method of any one of claims 1-81, wherein~~ the at least one anti-HER2 antibody is to be administered intravenously.

~~83. The method of any one of claims 1-82, wherein the at least one anti-HER2 antibody comprises one anti-HER2 antibody.~~

~~84~~22. The ~~use~~method of any one of claims 1-~~83~~21, wherein the at least one anti-HER2 antibody is trastuzumab, or a biosimilar thereof.

~~85. The method of any one of claims 1-83, wherein the at least one anti-HER2 antibody is trastuzumab.~~

~~86~~23. The ~~method~~use of any one of claims 1-~~76~~22, wherein the at least one anti-HER2 antibody comprises a first anti-HER2 antibody and a second anti-HER2 antibody.

~~87~~24. The ~~method~~use of claim ~~86~~23, wherein:

(a) the first anti-HER2 antibody is to be administered to the subject at a dose of ~~about~~ 4 mg/kg to ~~about~~ 10 mg/kg;

(b)

~~88. The method of claim 87, wherein the first anti-HER2 antibody is administered to the subject at a dose of about 6 mg/kg of the subject's body weight.~~

~~89. The method of claim 86, wherein the first anti-HER2 antibody is to be administered at a dose of ~~about~~ 200 mg to ~~about~~ 1,000 mg;:~~

~~(c)~~

~~90. The method of claim 89, wherein the first anti-HER2 antibody is administered at a dose of about 600 mg.~~

~~91. The method of any one of claims 86-90, wherein the second anti-HER2 antibody is to be administered to the subject at a dose of ~~about~~ 200 mg to ~~about~~ 1,000 mg;:~~

~~(d)~~

~~92. The method of claim 91, wherein the second anti-HER2 antibody is administered at a dose of about 420 mg.~~

~~93. The method of claim 91, wherein the second anti-HER2 antibody is administered at a dose of about 600 mg.~~

~~94. The method of claim 86, wherein the first anti-HER2 antibody is to be administered at a dose of about 6 mg/kg and the second anti-HER2 antibody is to be administered at a dose of about 420 mg;:~~

~~(e)~~

~~95. The method of any one of claims 86-94, wherein the first anti-HER2 antibody is to be administered intravenously;~~

~~(f) :~~

~~96. The method of any one of claims 86-94, wherein the first anti-HER2 antibody is to be administered subcutaneously;:~~

(g)

~~97. The method of any one of claims 86-96, wherein~~ the second anti-HER2 antibody is to be administered intravenously;

(h)

~~98. The method of any one of claims 86-96, wherein~~ the second anti-HER2 antibody is to be administered subcutaneously;

(i)

~~99. The method of claim 86, wherein~~ the first anti-HER2 antibody is to be administered at a dose of 6 mg/kg intravenously or at a dose of about 600 mg subcutaneously; and wherein the second anti-HER2 antibody is to be administered at a dose of about 420 mg intravenously; or

(i) :

~~100. The method of claim 86, wherein~~ the first anti-HER2 antibody and the second anti-HER2 antibody are to be administered in a pharmaceutical composition comprising about 600 mg of the first anti-HER2 antibody and 600 mg of the second anti-HER2 antibody; ~~wherein the pharmaceutical composition is~~ to be administered subcutaneously, optionally ;

~~101. The method of claim 100, wherein~~ the pharmaceutical composition further comprises hyaluronidase, further optionally ;

~~102. The method of claim 101, wherein~~ the pharmaceutical composition comprises about 20,000 units hyaluronidase.

~~103~~²⁵. The ~~method use~~ of claim 23 or claim 24~~any one of claims 86-102~~, wherein: (a) the first anti-HER2 antibody is trastuzumab, or a biosimilar thereof; and/or ;

~~104. The method of any one of claims 86-103, wherein~~ the second anti-HER2 antibody is pertuzumab, or a biosimilar thereof.

~~105. The method of any one of claims 86-104, wherein the first anti-HER2 antibody is administered about once every 3 weeks.~~

~~106. The method of any one of claims 86-105, wherein the second anti-HER2 antibody is administered about once every 3 weeks.~~

~~107. The method of any one of claims 1-106, wherein treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%.~~

~~108. The method of any one of claims 1-107, wherein treating the subject results in a TGI index of about 100%.~~

~~109. The method of any one of claims 1-108, wherein one or more therapeutic effects in the subject is improved after administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody to the subject relative to a baseline.~~

~~110. The method of claim 109, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the solid tumor, objective response rate, duration of response, time to response, progression free survival and overall survival.~~

~~111. The method of any one of claims 1-110, wherein the size of a tumor derived from the solid tumor 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 solid tumor before administration of the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody.~~

~~112. The method of any one of claims 1-111, wherein 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%.~~

~~113. The method of any one of claims 1-112, wherein the subject exhibits progression-free survival of 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 the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody.~~

~~114. The method of any one of claims 1-113, wherein the subject exhibits overall survival of 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 the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody.~~

~~115. The method of any one of claims 1-114, wherein 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 the tucatinib, or salt or solvate thereof, and the at least one anti-HER2 antibody.~~

~~116. The method of any one of claims 1-115, wherein the administration of the tucatinib, or salt or solvate thereof, increases the overall amount of HER2 in the solid tumor.~~

11726. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for A
~~method of~~ increasing the overall amount of HER2 in a solid tumor ~~comprising administering tucatinib, or salt or solvate thereof to a subject~~, wherein the administration of the tucatinib, or salt or solvate thereof, to a subject increases the overall amount of HER2 in the solid tumor.

~~118. The method of claim 116 or claim 117, wherein the overall amount of HER2 in the solid tumor is determined by Western blot analysis.~~

~~119. The method of any one of claims 1-118, wherein the administration of the tucatinib, or salt or solvate thereof, increases the amount of plasma membrane-bound HER2 in the solid tumor.~~

~~12027. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for A method of~~ increasing the amount of plasma membrane-bound HER2 in a solid tumor ~~comprising administering tucatinib, or salt or solvate thereof to a subject,~~ wherein the administration of the tucatinib, or salt or solvate thereof, to a subject increases the amount of plasma membrane-bound HER2 in the solid tumor.

~~121. The method of claim 119 or 120, wherein the amount of plasma membrane-bound HER2 in the solid tumor is determined by quantitative fluorescence-activated cell sorting (qFACS).~~

~~122. The method of any one of claims 1-121, wherein the administration of the tucatinib, or salt or solvate thereof, increases the dwell time of HER2 at the cell surface.~~

~~12328. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for A method of~~ increasing dwell time of HER2 at the cell surface of a solid tumor ~~comprising administering tucatinib, or salt or solvate thereof to a subject,~~ wherein the administration of the tucatinib, or salt or solvate thereof, to a subject increases the dwell time of HER2 at the cell surface.

~~124. The method of any one of claims 1-123, wherein the administration of the tucatinib, or salt or solvate thereof, increases the internalization of plasma membrane-bound HER2.~~

~~12529. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for A method of~~ increasing internalization of plasma membrane-bound HER2 in a solid tumor ~~comprising administering tucatinib, or salt or solvate thereof to a subject,~~ wherein the

administration of the tucatinib, or salt or solvate thereof, to a subject increases the internalization of plasma membrane-bound HER2.

~~126. The method of any one of claims 1-125, wherein the administration of the tucatinib, or salt or solvate thereof, increases the lysosomal degradation of HER2.~~

~~12730. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for A method of~~ increasing lysosomal degradation of HER2 in a solid tumor ~~comprising administering tucatinib, or salt or solvate thereof to a subject,~~ wherein the administration of the tucatinib, or salt or solvate thereof, to subject increases the lysosomal degradation of HER2.

~~12831. The method use~~ of any one of claims 1-~~12730~~, wherein the subject is a human.

~~12932. A kit comprising:~~

- (a) tucatinib, or salt or solvate thereof;
- (b) at least one anti-HER2 antibody; and
- (c) instructions for using the kit to treat a solid tumor in a subject ~~in the method of any one of claims 1-125.~~

~~130. The kit of claim 129, wherein the at least one anti-HER2 antibody comprises trastuzumab.~~

~~131. The kit of claim 129 or claim 130, wherein the at least one anti-HER2 antibody comprises pertuzumab.~~