[011a] In one aspect, the disclosure provides use of tucatinib in the manufacture of a first medicament and use of an anti-HER2 antibody-drug conjugate in the manufacture of a second medicament, wherein an effective amount of the first and second medicaments are to be used in combination therapy for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein:

following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months, or at least 7 months, or at least 7.5 months, or at least 8 months, or at least 9 months; or the subject exhibits an overall survival of at least eighteen months, or at least nineteen months, or at least twenty-two months, or at least twenty-six months, or at least thirty months; or

following administration of the combination therapy for twenty-four months, the subject has an estimated overall survival rate of greater than 35% or greater than 40%; or following administration of the combination therapy for thirty months, the subject has an estimated overall survival rate of greater than 30% or greater than 35%; or following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 40% or greater than 45%; or following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 25% or greater than 30%; or following administration of the combination therapy for fifteen months, the subject has an estimated progression-free survival rate of greater than 20% or greater than 25%; or wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 30% or greater than 40%; or

wherein the subject administered the combination therapy exhibits a greater than 40% reduction, or a greater than 45% reduction, or a greater than 50% reduction, in the risk of disease progression or death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone; or

wherein the subject administered the combination therapy exhibits a greater than 30% reduction in the risk of death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.

[012] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 7.5 months following administration of the combination therapy. For example, wherein the subject exhibits progression-free survival of at least eight months, at least nine months, or at least ten months following administration of the combination therapy.

[013] Also provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy, the subject exhibits an overall survival of at least eighteen months following administration of the combination therapy. For example, wherein the subject exhibits an overall survival of at least nineteen months, at least twenty-two months, at least twenty-six months, or at least thirty months following administration of the combination therapy.

[014] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy, the subject exhibits an overall survival of at least eighteen months following administration of the combination therapy. For example, wherein the subject exhibits an overall survival of at least nineteen months, at least twenty-two months, at least twenty-six months, or at least thirty months following administration of the combination therapy.

[015] In some of the ~~embodiment~~examples as provided herein, the subject has a brain metastasis.

[016] Accordingly, provided herein are methods of treating or ameliorating brain metastasis in a subject having HER2 positive breast cancer, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate. In some ~~embodiment~~examples, the time to additional intervention (e.g., radiation, surgery, or a combination thereof) for treatment of the brain metastasis in the subject has been increased. In some ~~embodiment~~examples, the need for additional intervention (e.g., radiation, surgery, or a combination thereof) for treatment of the brain metastasis in the subject has been prevented. In

some ~~embodiment~~examples, regression of an existing brain metastasis in the subject has been promoted. In some ~~embodiment~~examples, the size of an existing brain metastasis in the subject has been reduced.

[017] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine. In some ~~embodiment~~examples, the time to additional intervention (e.g., radiation, surgery, or a combination thereof) for treatment of the brain metastasis in the subject has been increased. In some ~~embodiment~~examples, the need for additional intervention (e.g., radiation, surgery, or a combination thereof) for treatment of the brain metastasis in the subject has been prevented. In some ~~embodiment~~examples, regression of an existing brain metastasis in the subject has been promoted. In some ~~embodiment~~examples, the size of an existing brain metastasis in the subject has been reduced.

[018] This disclosure also provides methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has brain metastasis, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months following administration of the combination therapy. For example, the subject can exhibit progression-free survival of at least seven months or at least nine months following administration of the combination therapy.

[019] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months following administration of the combination therapy. For example, the subject can exhibit progression-free survival of at least seven months or at least nine months following administration of the combination therapy.

[020] Methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof are also provided, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein the subject exhibits a greater than 40% reduction in the risk of disease progression or death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone. For

example, the subject can exhibit a greater than 45% reduction in the risk of disease progression or death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.

[021] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein the subject exhibits a greater than 40% reduction in the risk of disease progression or death as compared to a subject administered ado-trastuzumab emtansine alone. For example, the subject can exhibit a greater than 45% reduction in the risk of disease progression or death as compared to a subject administered ado-trastuzumab emtansine alone.

[022] Provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein the subject exhibits a greater than 30% reduction in the risk of death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.

[023] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein the subject exhibits a greater than 30% reduction in the risk of death as compared to a subject administered ado-trastuzumab emtansine alone.

[024] Also provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein the subject exhibits a greater than 50% reduction in the risk of disease progression or death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.

[025] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein the subject exhibits a greater than 50% reduction in the risk of disease progression or death as compared to a subject administered ado-trastuzumab emtansine alone.

[026] Further provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the methods comprising administering to the subject an

effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 40%. For example, wherein the subject has an estimated progression-free survival rate of greater than 45% following administration of the combination therapy for nine months.

[027] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 40%. For example, wherein the subject has an estimated progression-free survival rate of greater than 45% following administration of the combination therapy for nine months.

[028] This disclosure also provides methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 25%. For example, wherein the subject has an estimated progression-free survival rate of greater than 30% following administration of the combination therapy for twelve months.

[029] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 25%. For example, wherein the subject has an estimated progression-free survival rate of greater than 30% following administration of the combination therapy for twelve months.

[030] Methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof are provided herein, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for fifteen months, the subject has an estimated progression-free survival rate of greater than 20%. For example, wherein the subject

has an estimated progression-free survival rate of greater than 25% following administration of the combination therapy for fifteen months.

[031] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy for fifteen months, the subject has an estimated progression-free survival rate of greater than 20%. For example, wherein the subject has an estimated progression-free survival rate of greater than 25% following administration of the combination therapy for fifteen months.

[032] Provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for twenty-four months, the subject has an estimated overall survival rate of greater than 35%. For example, wherein the subject has an estimated overall survival rate of greater than 40% following administration of the combination therapy for twenty-four months.

[033] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy for twenty-four months, the subject has an estimated overall survival rate of greater than 35%. For example, wherein the subject has an estimated overall survival rate of greater than 40% following administration of the combination therapy for twenty-four months.

[034] Also provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for thirty months, the subject has an estimated overall survival rate of greater than 30%. For example, wherein the subject has an estimated overall survival rate of greater than 40% following administration of the combination therapy for thirty months.

[035] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy for thirty months, the subject has an estimated overall survival rate of greater than 30%. For example, wherein the subject has an estimated overall survival rate of greater than 40% following administration of the combination therapy for thirty months.

[036] Further provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 30%. For example, wherein the subject has an estimated progression-free survival rate of greater than 40% following administration of the combination therapy for nine months.

[037] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 30%. For example, wherein the subject has an estimated progression-free survival rate of greater than 40% following administration of the combination therapy for nine months.

[038] This disclosure also provides methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 15%. For example, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 20%.

[039] In some ~~embodiment~~examples, the methods comprise administering to the subject an effective amount of a combination therapy comprising tucatinib and ado-trastuzumab emtansine, wherein following administration of the combination therapy for twelve months, the subject has an

estimated progression-free survival rate of greater than 15%. For example, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 20%.

[040] Methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof are provided herein, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate and an effective amount of an anti-diarrheal agent. Also provided herein are method of reducing the severity or incidents of diarrhea, or preventing diarrhea in a subject having a HER2 positive breast cancer and being treated with an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, the method comprising administering an effective amount of an anti-diarrheal agent prophylactically. This disclosure also provides methods of reducing the likelihood of a subject developing diarrhea, wherein the subject has a HER2 positive breast cancer and is being treated with an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, the method comprising administering an effective amount of an anti-diarrheal agent prophylactically. In one aspect, the disclosure provides use of an anti-diarrheal agent for manufacturing a medicament for reducing the severity or incidents of diarrhea, or preventing diarrhea, or the likelihood developing diarrhea, in a subject having a HER2 positive breast cancer and being treated with an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein an effective amount of the medicament is to be administered prophylactically. In some such methods, the anti-HER2 antibody drug conjugate is ado-trastuzumab emtansine. In some such methods, the combination therapy and the anti-diarrheal agent can be administered concurrently. In some such methods, the anti-diarrheal agent is administered prior to administration of the combination therapy. In some ~~embodiment~~examples, the subject is exhibiting symptoms of diarrhea. In other ~~embodiment~~examples, the subject is not exhibiting symptoms of diarrhea.

[041] In some ~~embodiment~~examples, the tucatinib is administered twice daily. In some ~~embodiment~~examples, the HER2 positive breast cancer is unresectable or metastatic. In some ~~embodiment~~examples, the subject was previously treated with two or more anti-HER2-based regimens. In some ~~embodiment~~examples, the subject has not been previously treated with an anti-HER2 and/or an anti-EGFR tyrosine kinase inhibitor. In some ~~embodiment~~examples, the wherein the anti-HER2/EGFR tyrosine kinase inhibitor is selected from the group consisting of tucatinib, lapatinib, neratinib, or afatinib. In some ~~embodiment~~examples, the subject has not been previously treated with an anti-HER2 antibody-drug conjugate. In some ~~embodiment~~examples, the anti-HER2 antibody-drug conjugate is selected from the group consisting of ado-trastuzumab, or trastuzumab deruxtecan. In some ~~embodiment~~examples, the subject has not been previously treated with an anthracycline. In some ~~embodiment~~examples, the anthracycline is selected from

the group consisting of doxorubicin, epirubicin, mitoxantrone, idarubicin, liposomal doxorubicin, and combinations thereof.

[042] Also provided herein are methods for treating a HER2 positive breast cancer in a subject that has exhibited an adverse event after starting treatment with a combination therapy comprising tucatinib and anti-HER2 antibody-drug conjugate at an initial dosage level, comprising administering to the subject at least one component of the combination therapy at a reduced dosage level. In one aspect, the disclosure provides use of tucatinib in the manufacture of a first medicament and use of an anti-HER2 antibody-drug conjugate in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating a HER2 positive breast cancer in a subject that has exhibited an adverse event after starting treatment with a combination therapy comprising tucatinib and anti-HER2 antibody-drug conjugate at an initial dosage level, wherein at least one of the medicaments is to be administered to the subject at a reduced dosage level.

[043] In some ~~embodiment~~examples, the tucatinib is administered to the subject at an initial dose of about 150 mg to about 650 mg. In some ~~embodiment~~examples, the tucatinib is administered to the subject at an initial dose of about 300 mg. In some ~~embodiment~~examples, the tucatinib is administered to the subject at a reduced dose of about 125 mg to about 275 mg. In some ~~embodiment~~examples, the tucatinib is administered to the subject at a reduced dose of about 250 mg. In some ~~embodiment~~examples, the tucatinib is administered to the subject at a reduced dose of about 200 mg. In some ~~embodiment~~examples, the tucatinib is administered to the subject at a reduced dose of about 150. In some ~~embodiment~~examples, the anti-HER2 antibody-drug conjugate is administered to the subject at an initial dose of about 3 mg/kg to about 7 mg/kg.

[044] In some ~~embodiment~~examples, the anti-HER2 antibody-drug conjugate is trastuzumab deruxtecan. In some ~~embodiment~~examples, the anti-HER2 antibody-drug conjugate is ado-trastuzumab emtansine.

[045] In some ~~embodiment~~examples, the trastuzumab deruxtecan is administered to the subject at an initial dose of about 5.4 mg/kg. In some ~~embodiment~~examples, the trastuzumab deruxtecan is administered to the subject at a reduced dose of about 4.4 mg/kg. In some ~~embodiment~~examples, the trastuzumab deruxtecan is administered to the subject at a reduced dose of about 3.2 mg/kg.

[046] In some ~~embodiment~~examples, the ado-trastuzumab emtansine is administered to the subject at an initial dose of about 3.6 mg/kg. In some ~~embodiment~~examples, the ado-trastuzumab emtansine is administered to the subject at a reduced dose of about 3 mg/kg. In some ~~embodiment~~examples, the ado-trastuzumab emtansine is administered to the subject at a reduced dose of about 2.4 mg/kg.

[047] In some ~~embodiment~~examples, of any of the methods described herein, the ado-trastuzumab emtansine is administered to the subject at a reduced dose of about 2.4 mg/kg.

[048] In some ~~embodiment~~examples, of any of the methods described herein, the anti-HER2 antibody-drug conjugate is ado-trastuzumab emtansine.

[049] In some ~~embodiment~~examples, of any of the methods described herein, the anti-HER2 antibody-drug conjugate is trastuzumab deruxtecan.

[050] In some ~~embodiment~~examples, of any of the methods described herein, the trastuzumab deruxtecan is administered to the subject at a dose of about 3 mg/kg to about 7 mg/kg.

[051] In some ~~embodiment~~examples, of any of the methods described herein, the trastuzumab deruxtecan is administered to the subject at a dose of about 5.4 mg/kg.

[052] In some ~~embodiment~~examples, of any of the methods described herein, the trastuzumab deruxtecan is administered to the subject once per 21 day treatment cycle.

[053] In some ~~embodiment~~examples, of any of the methods described herein, the ado-trastuzumab emtansine is administered to the subject at a dose of about 3 mg/kg to about 7 mg/kg.

[054] In some ~~embodiment~~examples, of any of the methods described herein, the ado-trastuzumab emtansine is administered to the subject at a dose of about 3.6 mg/kg.

[055] In some ~~embodiment~~examples, of any of the methods described herein, the ado-trastuzumab emtansine is administered to the subject once per 21 day treatment cycle.

[056] In some ~~embodiment~~examples, of any of the methods described herein, wherein the administration of the tucatinib, or a salt or solvate thereof, increases the overall amount of HER2 in a solid tumor.

[057] In some ~~embodiment~~examples, of any of the methods described herein, wherein the overall amount of HER2 in the solid tumor is determined by western blot analysis.

[058] In some ~~embodiment~~examples, of any of the methods described herein, wherein the administration of the tucatinib, or a salt or solvate thereof, increases the amount of membrane-bound HER2 in the solid tumor.

[059] In some ~~embodiment~~examples, of any of the methods described herein, wherein the amount of membrane-bound HER2 in the solid tumor is determined by quantitative fluorescence activated cell sorting (qFACS).

[060] In some ~~embodiment~~examples, of any of the methods described herein, the administration of the tucatinib, or a salt or solvate thereof, increases a dwell time of HER2 at the cell surface.

[061] In some ~~embodiment~~examples, of any of the methods described herein, the administration of the tucatinib, or a salt or solvate thereof, increases an internalization of membrane-bound HER2.

[062] In some ~~embodiment~~examples, of any of the methods described herein, the administration of the tucatinib, or a salt or solvate thereof, increases a lysosomal degradation of HER2.

DESCRIPTION OF THE DRAWINGS

[063] FIG. 1 shows isobologram analysis of a 96-hour cytotoxicity assay.

[064] FIG. 2A shows the results of various treatments and combinations thereof in a BT-474 cell line-derived xenograft model.

[065] FIG. 2B shows the results of various treatments and combinations thereof in two HER2+ patient-derived (PDX) breast cancer models.

[066] FIG. 3 shows a summary of partial responses (PR) and complete responses (CR) in various cancer models following treatment with tucatinib, T-DMI1, and a combination of tucatinib and T-DM1.

[067] FIG. 4 illustrates a study schema for the clinical trial described in Example 3.

[068] FIG. 5 illustrates a pharmacokinetics (PK) sub-study as described in Example 3.

[069] FIG. 6 provides the amino acid sequence of the heavy (SEQ. ID NO. 1) and light chains (SEQ. ID NO. 2) of trastuzumab and the light chain variable domain (SEQ. ID NO. 3) and the heavy chain variable domain (SEQ. ID NO. 4) of trastuzumab.

[070] FIG. 7 shows a schematic of a proposed mechanism of action for tucatinib.

[071] FIG. 8 shows changes to total HER2 protein levels and HER2 membrane-bound protein levels upon treatment with tucatinib in various cancer cell lines.

[072] FIGS. 9A and 9B shows schematics of internalization assays using Trastuzumab-AF488 and Trastuzumab-QF.

What is claimed is:

~~1. A method of treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate.~~

~~2. A method of treating or ameliorating cancer in a subject in need thereof, the method comprising:~~

~~(a) identifying the subject as having a HER2 positive breast cancer; and~~

~~(b) administering to the subject a therapeutically effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate.~~

~~3~~1. Use of tucatinib in the manufacture of a first medicament and use of an anti-HER2 antibody-drug conjugate in the manufacture of a second medicament, wherein an effective amount of the first and second medicaments are to be used in combination therapy ~~A method~~ for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof~~, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate~~, wherein:

following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months, or at least 7 months, or at least 7.5 months, or at least 8 months, or at least 9 months; ~~following administration of the combination therapy~~or the subject exhibits an overall survival of at least eighteen months, or at least nineteen months, or at least twenty-two months, or at least twenty-six months, or at least thirty months; or

following administration of the combination therapy for twenty-four months, the subject has an estimated overall survival rate of greater than 35% or greater than 40%; or following administration of the combination therapy for thirty months, the subject has an estimated overall survival rate of greater than 30% or greater than 35%; or following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 40% or greater than 45%; or following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 25%

or greater than 30%; or following administration of the combination therapy for fifteen months, the subject has an estimated progression-free survival rate of greater than 20% or greater than 25%; or wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 30% or greater than 40%; or

wherein the subject administered the combination therapy exhibits a greater than 40% reduction, or a greater than 45% reduction, or a greater than 50% reduction, in the risk of disease progression or death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone; or

wherein the subject administered the combination therapy exhibits a greater than 30% reduction in the risk of death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.

~~4. The method of claim 3, wherein the subject exhibits progression-free survival of at least eight months following administration of the combination therapy.~~

~~5. The method of any one of claims 3 or 4, wherein the subject exhibits progression-free survival of at least nine months following administration of the combination therapy.~~

~~6. The method of any one of claims 3-5, wherein the subject exhibits progression-free survival of at least ten months following administration of the combination therapy.~~

~~7. The method of any one of claims 1-6, wherein the subject has a brain metastasis.~~

~~8. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy, the subject exhibits an overall survival of at least eighteen months following administration of the combination therapy.~~

~~9. The method of claim 8, wherein the subject exhibits an overall survival of at least nineteen months following administration of the combination therapy.~~

~~10. The method of any one of claims 8 or 9, wherein the subject exhibits an overall survival of at least twenty-two months following administration of the combination therapy.~~

~~11. The method of any one of claims 8-10, wherein the subject exhibits an overall survival of at least twenty-six months following administration of the combination therapy.~~

~~12. The method of any one of claims 8-11, wherein the subject exhibits an overall survival of at least thirty months following administration of the combination therapy.~~

~~13~~2. The ~~method~~use of ~~any one of claims 8-12~~claim 1, wherein the subject has a brain metastasis.

~~14. A method of treating or ameliorating a brain metastasis in a subject having HER2 positive breast cancer, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate.~~

~~15. The method of claim 14, wherein the time to additional intervention for treatment of the brain metastasis in the subject has been increased.~~

~~16. The method of any one of claims 14 or 15, wherein the need for additional intervention for treatment of the brain metastasis in the subject has been prevented.~~

~~17. The method of any one of claims 15 or 16, wherein the additional intervention is selected from the group consisting of radiation, surgery, and a combination thereof.~~

~~18~~3. The ~~method~~use ~~of any one~~ of claim~~s 14-17~~2, wherein regression of an existing brain metastasis in the subject has been promoted by the medicament; and/or wherein the size of an existing brain metastasis in the subject has been reduced by the medicament.

~~19. The method of any one of claims 14-18, wherein the size of an existing brain metastasis in the subject has been reduced.~~

~~20. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months following administration of the combination therapy.~~

~~21. The method of claim 20, wherein the subject exhibits progression-free survival of at least seven months following administration of the combination therapy.~~

~~22. The method of any one of claims 20 or 21, wherein the subject exhibits progression free survival of at least nine months following administration of the combination therapy.~~

~~23. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti HER2 antibody-drug conjugate, wherein the subject exhibits a greater than 40% reduction in the risk of disease progression or death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.~~

~~24. The method of claim 23, wherein the subject administered the combination therapy comprising tucatinib and the anti-HER2 antibody drug conjugate exhibits a greater than 45% reduction in the risk of disease progression or death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.~~

~~25. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein the subject~~

~~exhibits a greater than 30% reduction in the risk of death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.~~

~~26. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein the subject exhibits a greater than 50% reduction in the risk of disease progression or death as compared to a subject administered the anti-HER2 antibody-drug conjugate alone.~~

~~27. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti HER2 antibody-drug conjugate, wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 40%.~~

~~28. The method of claim 27, wherein the subject has an estimated progression-free survival rate of greater than 45%.~~

~~29. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 25%.~~

~~30. The method of claim 29, wherein the subject has an estimated progression-free survival rate of greater than 30%.~~

~~31. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following~~

~~administration of the combination therapy for fifteen months, the subject has an estimated progression-free survival rate of greater than 20%.~~

~~32. The method of claim 31, wherein the subject has an estimated progression free survival rate of greater than 25%.~~

~~33. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti HER2 antibody-drug conjugate, wherein following administration of the combination therapy for twenty four months, the subject has an estimated overall survival rate of greater than 35%.~~

~~34. The method of claim 33, wherein the subject has an estimated overall survival rate of greater than 40%.~~

~~35. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for thirty months, the subject has an estimated overall survival rate of greater than 30%.~~

~~36. The method of claim 35, wherein the subject has an estimated overall survival rate of greater than 40%.~~

~~37. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 30%.~~

~~38. The method of claim 37, wherein the subject has an estimated progression-free survival rate of greater than 40%.~~

~~39. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 15%.~~

~~40. The method of claim 39, wherein the subject has an estimated progression-free survival rate of greater than 20%.~~

~~41. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate and an effective amount of an anti-diarrheal agent.~~

~~42. The method of claim 41, wherein the combination therapy and the anti-diarrheal agent are administered concurrently.~~

~~43. The method of claim 42, wherein the anti-diarrheal agent is administered prior to administration of the combination therapy.~~

~~44. The method of claim 41-43, wherein the subject is exhibiting symptoms of diarrhea.~~

~~45. The method of claim 41-43, wherein the subject is not exhibiting symptoms of diarrhea.~~

~~46~~4. Use of an anti-diarrheal agent for manufacturing a medicament for ~~A method of~~ reducing the severity or incidents of diarrhea, or preventing diarrhea, or the likelihood developing diarrhea, in a subject having a HER2 positive breast cancer and being treated with an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, ~~the method~~

~~comprising administering~~ wherein an effective amount of ~~an anti-diarrheal agent~~the medicament is to be administered prophylactically.

~~47~~5. The ~~method~~ use of claim ~~46~~4, wherein the combination therapy and the anti-diarrheal agent are to be administered concurrently.

~~48~~6. The ~~method~~ use of claim ~~46~~4, wherein the anti-diarrheal agent is to be administered prior to administration of the combination therapy.

~~49. A method of reducing the likelihood of a subject developing diarrhea, wherein the subject has a HER2 positive breast cancer and is being treated with an effective amount of a combination therapy comprising tucatinib and an anti-HER2 antibody-drug conjugate, the method comprising administering an effective amount of an anti-diarrheal agent prophylactically.~~

~~50. The method of claim 49, wherein the combination therapy and the anti-diarrheal agent are administered concurrently.~~

~~51. The method of claim 49, wherein the anti-diarrheal agent is administered prior to administration of the combination therapy.~~

~~52. The method of any one of claims 1-51, wherein the tucatinib is administered to the subject at a dose of about 150 mg to about 650 mg.~~

~~53. The method of claim 52, wherein the tucatinib is administered to the subject at a dose of about 300 mg.~~

~~54. The method of claim 52 or 53, wherein the tucatinib is administered once or twice per day.~~

~~55. The method of any one of claims 1-54, wherein the tucatinib is administered twice daily.~~

~~56. The method of claim 55, wherein the tucatinib is administered to the subject at a dose of about 300 mg twice per day.~~

~~57. The method of any one of claims 1-56, wherein the tucatinib is administered to the subject orally.~~

~~58~~7. The ~~method~~use of any one of claims 1-~~57~~6, wherein the anti-HER2 antibody-drug conjugate is to be administered to the subject at a dose of about 150 mg to about 400 mg.

~~59~~8. The ~~method~~use of claim ~~58~~7, wherein the anti-HER2 antibody-drug conjugate is to be administered to the subject at a dose of about 200 mg.

~~60. The method of claim 58 or 59, wherein the anti-HER2 antibody-drug conjugate is administered to the subject subcutaneously.~~

~~61~~9. The ~~method~~use of any one of claims 1-~~60~~8, wherein the anti-HER2 antibody-drug conjugate is to be administered to the subject at a dose of about 1 mg/kg to about 5 mg/kg.

~~62~~10. The ~~method~~use of claim ~~61~~9, wherein the anti-HER2 antibody-drug conjugate is to be administered to the subject at a dose of about 3.6 mg/kg; or at a dose of about 4 mg/kg.

~~63. The method of claim 61, wherein the anti-HER2 antibody-drug conjugate is administered to the subject at a dose of about 4 mg/kg.~~

~~64~~11. The ~~method~~use of claim ~~61~~10, wherein the anti-HER2 antibody-drug conjugate is to be administered to the subject at an initial dose of about 4 mg/kg followed by subsequent doses of about 3.6 mg/kg.

~~65. The method of any one of claims 61-64, wherein the anti-HER2 antibody-drug conjugate is administered intravenously.~~

~~66. The method of any one of claims 1-65, wherein the anti-HER2 antibody-drug conjugate is administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, or once about every 4 weeks.~~

~~67. The method of claim 66, wherein the anti-HER2 antibody-drug conjugate is administered once about every 3 weeks.~~

~~68~~12. The ~~method~~use of any one of claims 1-~~67~~11, wherein the tucatinib and the anti-HER2 antibody-drug conjugate are to be administered to the subject on a 21 day treatment cycle.

~~69~~13. The ~~method~~use of claim ~~68~~12, wherein the tucatinib is to be administered to the subject twice per day on each day of the 21 day treatment cycle.

~~70~~14. The ~~method~~use of any one of claims ~~68~~12-~~69~~13, wherein the anti-HER2 antibody-drug conjugate is to be administered to the subject once per 21 day treatment cycle.

~~71~~15. The ~~method~~use of claim ~~70~~14, wherein the dose of the anti-HER2 antibody-drug conjugate during the first 21 day treatment cycle is 4 mg/kg and the dose of the anti-HER2 antibody-drug conjugate during the subsequent 21 day treatment cycles is 3.6 mg/kg.

~~72~~16. The ~~method~~use of any one of claims 1-~~71~~15, wherein the HER2 positive breast cancer is unresectable or metastatic.

~~73~~17. The ~~method~~use of any one of claims 1-~~72~~16, wherein the subject was previously treated with at least one anticancer therapy.

~~74~~18. The ~~method~~use of claim ~~73~~17, wherein the least one anticancer therapy is an anti-HER2 antibody or anti-HER2 antibody-drug conjugate.

~~75~~19. The ~~method~~use of claim ~~73~~17, wherein the at least one previous anticancer therapy is selected from the group consisting of trastuzumab, trastuzumab and a taxane, pertuzumab, ado-trastuzumab, and combinations thereof.

~~76. The method of any one of claims 73-75, wherein the subject is refractory to the previous anticancer therapy.~~

~~77. The method of claim 71-76, wherein the subject developed a brain metastasis during the previous anticancer therapy.~~

~~78. The method of any one of claims 1-77, wherein the subject has not been treated with another therapeutic agent for the breast cancer within the past 12 months.~~

~~79. The method of any one of claims 1-78, wherein the subject was previously treated with two or more anti-HER2-based regimens.~~

~~80. The method of any one of claims 1-79, wherein the subject has not previously been treated with another therapeutic agent for the breast cancer.~~

~~81. The method of any one of claims 1-80, wherein the subject has not previously been treated with lapatinib, neratinib, afatinib, or capecitabine.~~

~~82. The method of any one of claims 1-81, wherein the subject has not been previously treated with an anti-HER2 and/or an anti-EGFR tyrosine kinase inhibitor.~~

~~83. The method of claim 82, wherein the wherein the anti-HER2/EGFR tyrosine kinase inhibitor is selected from the group consisting of tucatinib, lapatinib, neratinib, or afatinib.~~

~~84. The method of any one of claims 1-83, wherein the subject has not been previously treated with an anti-HER2 antibody-drug conjugate.~~

~~85. The method of claim 84, wherein the anti-HER2 antibody-drug conjugate is selected from the group consisting of ado-trastuzumab, or trastuzumab deruxtecan.~~

~~86. The method of any one of claims 1-85, wherein the subject has not been previously treated with an anthracycline.~~

~~87. The method of claim 86, wherein the anthracycline is selected from the group consisting of doxorubicin, epirubicin, mitoxantrone, idarubicin, liposomal doxorubicin, and combinations thereof.~~

~~88~~20. Use of tucatinib in the manufacture of a first medicament and use of an anti-HER2 antibody-drug conjugate in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy~~A method~~ for treating a HER2 positive breast cancer in a subject that has exhibited an adverse event after starting treatment with a combination therapy comprising tucatinib and anti-HER2 antibody-drug conjugate at an initial dosage level, ~~comprising~~ wherein at least one of the medicaments is to be administered ~~administering~~ to the subject ~~at least one component of the combination therapy~~ at a reduced dosage level.

~~89~~21. The ~~method~~use of claim ~~88~~20, wherein the tucatinib is to be administered to the subject at an initial dose of about 150 mg to about 650 mg; wherein the tucatinib is to be administered to the subject at a reduced dose of about 125 mg to about 275 mg.

~~90. The method of any one of claims 88 or 89, wherein the tucatinib is administered to the subject at an initial dose of about 300 mg.~~

~~91. The method of any one of claims 88-90, wherein the tucatinib is administered to the subject at a reduced dose of about 125 mg to about 275 mg.~~

~~92. The method of any one of claims 88-91, wherein the tucatinib is administered to the subject at a reduced dose of about 250 mg.~~

~~93. The method of any one of claims 88-91, wherein the tucatinib is administered to the subject at a reduced dose of about 200 mg.~~

~~94. The method of any one of claims 88-91, wherein the tucatinib is administered to the subject at a reduced dose of about 150.~~

~~95~~22. The ~~method~~use of claim ~~88-94~~20 or 21, wherein the anti-HER2 antibody-drug conjugate is to be administered to the subject at an initial dose of about 3 mg/kg to about 7 mg/kg.

~~96~~23. The ~~method~~use of any one of claims ~~88-95~~1-22, wherein the anti-HER2 antibody-drug conjugate is trastuzumab deruxtecan or ado-trastuzumab emtansine.

~~97. The method of any one of claims 88-95, wherein the anti-HER2 antibody-drug conjugate is ado-trastuzumab emtansine.~~

~~98~~24. The ~~method~~use of claim ~~96~~23, wherein the trastuzumab deruxtecan is to be administered to the subject at an initial dose of about 5.4 mg/kg or about 3.6 mg/kg, and at a reduced dose of about 4.4 mg/kg or about 3.2 mg/kg; or wherein the ado-trastuzumab emtansine is to be administered to the subject at an initial dose of about 3.6 mg/kg and at a reduced dose of about 3 mg/kg or about 2.4 mg/kg.

~~99. The method of claim 96 or 98, wherein the trastuzumab deruxtecan is administered to the subject at a reduced dose of about 4.4 mg/kg.~~

~~100. The method of claim 96 or 98, wherein the trastuzumab deruxtecan is administered to the subject at a reduced dose of about 3.2 mg/kg.~~

~~101. The method of claim 97, wherein the ado-trastuzumab emtansine is administered to the subject at an initial dose of about 3.6 mg/kg.~~

~~102. The method of claim 97 or 101, wherein the ado-trastuzumab emtansine is administered to the subject at a reduced dose of about 3 mg/kg.~~

~~103. The method of claim 97 or 101, wherein the ado-trastuzumab emtansine is administered to the subject at a reduced dose of about 2.4 mg/kg.~~

~~104. The method of any one of claims 1-95, wherein the anti-HER2 antibody-drug conjugate is ado-trastuzumab emtansine.~~

~~105. The method of any one of claims 1-95, wherein the anti-HER2 antibody-drug conjugate is trastuzumab deruxtecan.~~

~~106. The method of any one of claims 1-105, wherein the administration of the tucatinib, or a salt or solvate thereof, increases the overall amount of HER2 in a solid tumor.~~

~~107. The method of claim 106, wherein the overall amount of HER2 in the solid tumor is determined by western blot analysis.~~

~~108. The method of any one of claims 1-107, wherein the administration of the tucatinib, or a salt or solvate thereof, increases the amount of membrane-bound HER2 in a solid tumor.~~

~~109. The method of claim 108, wherein the amount of membrane-bound HER2 in the solid tumor is determined by quantitative fluorescence activated cell sorting (qFACS).~~

~~110. The method of any one of claims 1-109, wherein the administration of the tucatinib, or a salt or solvate thereof, increases dwell time of HER2 at the cell surface.~~

~~111. The method of any one of claims 1-110, wherein the administration of the tucatinib, or a salt or solvate thereof, increases internalization of membrane-bound HER2.~~

~~112. The method of any one of claims 1-111, wherein the administration of the tucatinib, or a salt or solvate thereof, increases lysosomal degradation of HER2.~~