[0008] 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

[0008a] In one aspect of the present disclosure, there is provided a use of a composition comprising a therapeutically effective amount of tucatinib for the manufacture of a medicament for the treatment of breast cancer in a subject; wherein the subject to be treated is not concurrently receiving treatment with:

(a) a therapeutically effective amount of a compound that modulates the activity of a cytochrome p450 protein;

(b) a therapeutically effective amount of a substrate of a cytochrome p450 protein; or

(c) a therapeutically effective amount of a substrate of P-glycoprotein (P-gp).

[0009] Also provided herein is a method for treating breast cancer in a subject comprising administering a therapeutically effective amount of tucatinib, or salt or solvate thereof, to the subject, wherein the subject is not concurrently receiving treatment with a therapeutically effective amount of a substrate of a multidrug and toxin extrusion (MATE) protein. In some examples, the subject has not received treatment with the substrate of the MATE protein within the past 7 days. In some examples, the subject has not received treatment with the substrate of the MATE protein within the past 3 months. In some examples, the subject has not received treatment with the substrate of the MATE protein within the past 12 months. In some examples, the subject has not previously received treatment with the substrate of the MATE protein. In some of any of the examples herein, the MATE protein is MATE1. In some of any of the examples herein, the MATE protein is MATE2K. In some of any of examples herein, the substrate of the MATE protein is selected from the group consisting of metformin, oxazolidinone, fexofenadine, tetraethylammonium (TEA), N-methylphenylpyridinium (MPP+), paraquat, agmatine, cimetidine, procainamide, pramipexole, atenolol, serotonin, quinidine, verapamil, cisplatin, oxaliplatin, and pyrimethamine.

[0010] Also provided herein is a method for treating breast cancer in a subject comprising administering a therapeutically effective amount of tucatinib, or salt or solvate thereof, to the subject, wherein the subject is not concurrently receiving treatment with a therapeutically effective amount of a substrate of an organic cation transporter (OCT). In some examples, the subject has not received treatment with the substrate of the OCT within the past 7 days. In some examples, the subject has not received treatment with the substrate of the OCT within the past 3 months. In some examples, the subject has not received treatment with the substrate of the OCT protein within the past 12 months. In some examples, the subject has not previously received treatment with the substrate of the OCT. In some of any of the examples herein, the OCT is OCT1. In some of any of the examples herein, the OCT is

OCT2. In some of any of the examples herein, is selected from the group consisting of metformin, oxazolidinone, fexofenadine, tetraethylammonium (TEA), N-methylphenylpyridinium (MPP+), paraquat, agmatine, cimetidine, procainamide, pramipexole, atenolol, serotonin, quinidine, verapamil, cisplatin, oxaliplatin, and pyrimethamine.

[0011] Also provided herein is a method for treating breast cancer in a subject comprising administering a therapeutically effective amount of tucatinib, or salt or solvate thereof, to the subject, wherein the subject does not have impaired renal function. In some examples, the subject has not had impaired renal function within the past 12 months. In some of any of the examples herein, impaired renal function is determined based on the serum creatinine level in the subject. In some of any of the examples herein, impaired renal function is determined based on the serum creatinine level in the subject. In some examples, the subject is male and the subject has a serum creatinine level of less than 1.5 mg/dL or the subject is female and has a serum creatinine level of less than to 1.4 mg/dL. In some of any of the examples herein, impaired renal function is determined based on the subject having abnormal creatinine clearance. In some of any of the examples herein, impaired renal function is determined based on the glomerular filtration rate of the subject.

[0012] Also provided herein is a method for treating breast cancer in a subject comprising administering a therapeutically effective amount of tucatinib, or salt or solvate thereof, to the subject, wherein the subject is not concurrently receiving treatment with a therapeutically effective amount of a compound that modulates the activity of a cytochrome p450 protein. In some examples, the subject has not received treatment with the compound that modulates the activity of the cytochrome p450 protein within the past 7 days. In some examples, the subject has not received treatment with the compound that modulates the activity of the cytochrome p450 protein within the past 3 months. In some examples, the subject has not received treatment with the compound that modulates the activity of the cytochrome p450 protein within the past 12 months. In some examples, the subject has not previously received treatment with compound that modulates the activity of the cytochrome p450 protein. In some of any of the examples herein, the compound that modulates the activity of the cytochrome p450 protein is an inhibitor of the activity of the cytochrome p450 protein. In some of any of the examples herein, the compound that modulates the activity of the cytochrome p450 protein is a strong

inhibitor of the activity of the cytochrome p450 protein. In some of any of the examples herein, the compound that modulates the activity of the cytochrome p450 protein is an inducer of the activity of the cytochrome p450 protein. In some of any of the examples herein, the compound that modulates the activity of the cytochrome p450 protein is a strong inducer of the activity of the cytochrome p450 protein.

[0013] Also provided herein is a method for treating breast cancer in a subject comprising administering a therapeutically effective amount of tucatinib, or salt or solvate thereof, to the subject, wherein the subject is not concurrently receiving treatment with a therapeutically effective amount of a substrate of a cytochrome p450 protein. In some examples, the subject has not received treatment with the substrate of the cytochrome p450 protein within the past 7 days. In some examples, the subject has not received treatment with the substrate of the cytochrome p450 protein within the past 3 months. In some examples, the subject has not received treatment with the substrate of the cytochrome p450 protein within the past 12 months. In some examples, the subject has not previously received treatment with the substrate of the cytochrome p450 protein. In some of any of the examples herein, the substrate of the cytochrome p450 protein is a sensitive CYP3A substrate.

[0014] Also provided herein is a method for treating breast cancer in a subject comprising administering a therapeutically effective amount of tucatinib, or salt or solvate thereof, to the subject, wherein the subject is not concurrently receiving treatment with a therapeutically effective amount of a substrate of P-glycoprotein (P-gp). In some examples, the subject has not received treatment with the substrate of P-gp within the past 7 days. In some examples, the subject has not received treatment with the substrate of P-gp within the past 3 months. In some examples, the subject has not received treatment with the substrate of P-gp within the past 12 months. In some examples, the subject has not previously received treatment with substrate of P-gp. In some of any of the examples herein, the substrate of P-gp is a substrate with a narrow therapeutic index.

[0015] In some of any of the examples herein, the tucatinib is administered to the subject at a dose of about 150 mg to about 650 mg. In some of any of the examples herein, the tucatinib is administered to the subject at a dose of about 300 mg. In some of any of the

examples herein, the tucatinib is administered once or twice per day. In some of any of the examples herein, the tucatinib is administered to the subject at a dose of about 300 mg twice per day. In some of any of the examples herein, the tucatinib is administered to the subject orally.

[0016] In some of any of the examples herein, the breast cancer is a HER2 positive breast cancer. In some examples, the cancer is determined to be HER2 positive using *in situ* hybridization, fluorescence *in situ* hybridization, or immunohistochemistry. In some of any of the examples herein, the breast cancer is metastatic. In some examples, the breast cancer has metastasized to the brain. In some of any of the examples herein, the breast cancer is locally advanced. In some of any of the examples herein, the breast cancer is unresectable.

[0017] In some of any of the examples herein, the method further comprises administering one or more additional therapeutic agents to the subject to treat the breast cancer. In some examples, the one or more additional therapeutic agents is selected from the group consisting of capecitabine and an anti-HER2 antibody, such as trastuzumab. In some examples, the capecitabine is administered to the subject orally. In some of any of the examples herein, the capecitabine is administered to the subject twice per day. In some examples, the trastuzumab is administered subcutaneously or intravenously. In some examples the trastuzumab is administered once about every 3 weeks.

[0018] In some of any of the examples herein, the subject has been previously treated with one or more additional therapeutic agents for the breast cancer. In some examples, the one or more additional therapeutic agents is an anti-HER2 antibody or anti-HER2 antibody-drug conjugate. In some of any of the examples herein, the subject has not been treated with another therapeutic agent for the breast cancer within the past 12 months. In some of any of the examples herein, the subject has not previously been treated with another therapeutic agent for the breast cancer.

[0019] In some of any of the examples herein, treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%, such as about 100%. In some of any of the examples herein, one or more therapeutic effects in the subject is improved after administration of tucatinib to the subject relative to a baseline. In some examples, the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from

the breast cancer, objective response rate, duration of response, time to response, progression free survival and overall survival. In some of any of the examples herein, the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIG. 1 shows the schedule of treatment and assessments of the Phase I clinical study described in Example 1.

[0021] FIG. 2 is a graph showing the mean (± SD) plasma metformin concentration versus time profile for subjects treated with metformin alone or metformin in combination with tucatinib.

[0022] FIG. 3 is a graph showing the mean (± SD) plasma iohexol concentrations versus time profile for subjects treated with metformin alone or metformin in combination with tucatinib.

[0023] FIG. 4 is a graph showing the mean (± SD) plasma tucatinib trough concentration versus time.

[0024] FIG. 5 shows the schedule of treatment and assessments of Part A of the Phase I clinical study described in Example 2.

[0025] FIG. 6 shows the schedule of treatment and assessments of Part B of the Phase I clinical study described in Example 2.

[0026] FIG. 7 shows the schedule of treatment and assessments of Part C of the Phase I clinical study described in Example 2.

[0027] FIG. 8 shows the schedule of treatment and assessments of Part D of the Phase I clinical study described in Example 2.

[0028] FIG. 9 shows the schedule of treatment and assessments of Part E of the Phase I clinical study described in Example 2.

CLAIMS

What is claimed is:

1. Use of a composition comprising a therapeutically effective amount of tucatinib for the manufacture of a medicament for the treatment of breast cancer in a subject; wherein the subject to be treated is not concurrently receiving treatment with:

(a) a therapeutically effective amount of a compound that modulates the activity of a cytochrome p450 protein;

(b) a therapeutically effective amount of a substrate of a cytochrome p450 protein; or

(c) a therapeutically effective amount of a substrate of P-glycoprotein (P-gp).

2. The use of claim 1, wherein:

(a) the subject to be treated has not received treatment with the compound or substrate within the past 7 days before treatment;

(b) the subject has not received treatment with the compound or substrate within the past 3 months before treatment;

(c) the subject has not received treatment with the compound or substrate within the past 12 months before treatment;

(d) the subject has not received treatment with the compound or substrate previously.

3. The use of claim 1 or claim 2, wherein the compound that modulates the activity of the cytochrome p450 protein is an inhibitor of the activity of the cytochrome p450 protein; optionally wherein the inhibitor is a strong inhibitor; optionally wherein:

(a) the cytochrome p450 protein is CYP3A4; optionally wherein the compound that inhibits the activity of CYP3A4 is itraconazole; or

(b) the cytochrome p450 protein is CYP2C8, optionally wherein the compound that inhibits the activity of CYP2C8 is gemfibrozil.

4. The use of claim 1 or claim 2, wherein the compound that modulates the activity of the cytochrome p450 protein is an inducer of the activity of the cytochrome p450 protein; optionally wherein the inducer is a strong inducer; optionally wherein the compound is rifampin.

5. The use of claim 1 or claim 2, wherein the cytochrome p450 protein is CYP3A4 or CYP2C8; optionally wherein the substrate of the cytochrome p450 protein is selected from the group consisting of budesonide, buspirone, eplerenone, eletriptan, felodipine, fluticasone, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam, and vardenafil

6. The use of claim 1 or claim 2, wherein the substrate of P-gp is selected from the group consisting of amitriptyline, carbamazepine, clonidine, cyclosporine, digitoxin, digoxin, imipramine, phenobarbital, phenytoin, quinidine, rifampicin, sirolimus, tacrolimus, temsirolimus, trimipramine, vincristine, paclitaxel, and dabigatran etexilate.

7. The use of any one of claims 1-6, wherein:

(a) the therapeutically effective amount of tucatinib to be administered to the subject is at a dose of about 150 mg to about 650 mg;

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

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

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

8. The use of any one of claims 1-7, wherein the breast cancer is a HER2 positive breast cancer; optionally wherein the cancer is determined to be HER2 positive using *in situ* hybridization, fluorescence *in situ* hybridization, or immunohistochemistry.

9. The use of any one of claims 1-8, wherein the breast cancer is metastatic; optionally wherein the breast cancer has metastasized to the brain.

10. The use of any one of claims 1-9, wherein the breast cancer is locally advanced and/or unresectable.

11. The use of any one of claims 1-10, wherein one or more additional therapeutic agents is to be further administered to the subject to treat the breast cancer; optionally wherein the one or more additional therapeutic agents is selected from the group consisting of capecitabine and an anti-HER2 antibody; optionally wherein the anti-HER2 antibody is trastuzumab; optionally wherein the one or more additional therapeutic agents are capecitabine and trastuzumab.

12. The use of claim 11, wherein the one or more additional therapeutic agents comprise capecitabine, wherein the capecitabine is to be administered to the subject at a dose of about 500 mg/m^2 to about 1500 mg/m^2; optionally wherein the capecitabine is to be administered to the subject at a dose of about 1000 mg/m^2; optionally wherein the capecitabine is to be administered to the subject orally; optionally wherein the capecitabine is to be administered to the subject twice per day.

13. The use of claim 11 or claim 12, wherein the one or more additional therapeutic agents comprise trastuzumab, wherein:

(a) the trastuzumab is to be administered to the subject at a dose of about 400 mg to about 800 mg, optionally wherein the trastuzumab is to be administered to the subject at a dose of about 600 mg;

(b) the trastuzumab is to be administered to the subject at a dose of about 4 mg/kg to about 10 mg/kg, optionally about 8 mg/kg;

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

(d) the trastuzumab is to be administered to the subject subcutaneously;

(e) the trastuzumab is to be administered to the subject intravenously;

(f) the trastuzumab is to be administered to the subject once about every 1 week, once about every 2 weeks, once about every 3 weeks, or once about every 4 weeks.

14. The use of claim 13, wherein tucatinib, capecitabine, and trastuzumab are to be administered to the subject on a 21 day treatment cycle; optionally wherein the tucatinib is to be administered to the subject twice per day on each day of the 21 day treatment cycle; optionally

wherein the capecitabine is to be administered to the subject twice per day on each of days 1-14 of the 21 day treatment cycle; optionally wherein the trastuzumab is to be administered to the subject once per 21 day treatment cycle, optionally wherein the dose of trastuzumab during the first 21 day treatment cycle is 8 mg/kg and the dose of trastuzumab during the subsequent 21 day treatment cycles is 6 mg/kg.

15. The use of any one of claims 1-14, wherein the subject to be treated has been previously treated with one or more additional therapeutic agents for the breast cancer; optionally wherein the one or more additional therapeutic agents is an anti-HER2 antibody or anti-HER2 antibody-drug conjugate

16. The use of claim 15, wherein the one or more additional therapeutic agents is trastuzumab, pertuzumab, and/or T-DM1.

17. The use of any one of claims 1-16, wherein the subject to be treated has not been treated with another therapeutic agent for the breast cancer within the past 12 months; optionally wherein the subject to be treated has not previously been treated with another therapeutic agent for the breast cancer; optionally wherein the subject has not previously been treated with lapatinib, neratinib, afatinib, or capecitabine.

18. The use of any one of claims 1-17, wherein treating the subject results in a tumor growth inhibition (TGI) index of at least 85%; optionally wherein treating the subject results in a TGI index of about 100%.

19. The use of any one of claims 1-18, wherein one or more therapeutic effects in the subject is improved after administration of tucatinib to the subject relative to a baseline; optionally wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the breast cancer, objective response rate, duration of response, time to response, progression free survival and overall survival.

20. The use of any one of claims 1-19, wherein the subject is a human.