

CLAIMS

1. ~~A method of~~ Use of tucatinib in the manufacture of a medicament for use in combinatorial therapy for treating a HER2 positive cancer in a subject in need thereof, ~~the method comprising administering to the subject a therapeutically effective amount of a combination therapy comprising tucatinib,~~ wherein said medicament is to be administered in combination with trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist.
2. Use of tucatinib in the manufacture of a medicament for use in combinatorial therapy for A ~~method of~~ treating cancer in a subject in need thereof, the ~~method-use~~ comprising:
 - (a) identifying the subject as having a HER2 positive cancer; and
 - (b) ~~administering to~~ wherein the subject is to be administered a therapeutically effective amount of a combination therapy comprising ~~tucatinib~~ the medicament, trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist.
3. The ~~use method~~ of any one of claims 1 or 2, wherein the trastuzumab is to be administered to the subject at a dose of about 6 mg/kg; or
4. ~~The method of any one of claims 1 or 2,~~ wherein the trastuzumab is to be administered to the subject at a dose of about 4 mg/kg.
54. The ~~use method~~ of any one of claims 1-43, wherein the tucatinib is to be administered to the subject at a dose of about 150 mg to about 650 mg.
65. The ~~use method~~ of any one of claims 1-54, wherein the tucatinib is to be administered twice daily.
7. ~~The method of any one of claims 1-6, wherein the tucatinib is administered to the subject orally.~~

~~86.~~ The ~~method-use~~ of any one of claims 1-~~75~~, wherein the VEGFR-2 antagonist is selected from the group consisting of bevacizumab, ramucirumab, aflibercept, cetuximab, panitumumab, regorafenib, sunitinib, sorafenib, pazopanib, vandetanib, axitinib, cediranib, vatalanib, motesanib, lucatinib, intedanib, semaxanib, apatinib, lenvatinib, carbozantinib, and a combination thereof.

~~97.~~ The ~~usemethod~~ of any one of claims 1-~~86~~, wherein the VEGFR-2 antagonist is a monoclonal antibody selected from the group consisting of bevacizumab, ramucirumab, aflibercept, cetuximab, panitumumab, and combinations thereof.

~~108.~~ The ~~usemethod~~ of any one of claims 1-~~97~~, wherein the VEGFR-2 antagonist is ramucirumab.

~~11.~~ The method of claim ~~10~~, and wherein the ramucirumab is to be administered to the subject at a dose of about 8 mg/kg.

~~129.~~ The ~~usemethod~~ of any one of claims 1-~~11~~8 wherein the taxane is selected from the group consisting of paclitaxel, docetaxel, cabazitaxel, larotaxel, BMS-184476, BMS-188797, BMS-275183, milataxel, ortaxel, TL-310, docosahexaenoic acid-paclitaxel (DHA-paclitaxel), nab paclitaxel, EndoTAG+paclitaxel, XRP9881, polymeric-micellar paclitaxel, RPR-109881A, a pharmaceutically acceptable salt or solvate thereof, and a combination thereof.

~~1310.~~ The ~~usemethod~~ of ~~any one of claims 1-12~~claim 9, wherein the taxane is paclitaxel. and

~~14.~~ The method of claim ~~13~~, wherein the paclitaxel is to be administered to the subject at a dose of about 50 mg/m² to about 100 mg/m², optionally

~~15.~~ The method of ~~any one of claims 12-14~~, wherein the paclitaxel is to be administered to the subject at a dose of about 80 mg/m².

~~16~~11. The usemethod of any one of claims 1-~~15~~10, wherein the HER2 positive cancer is selected from the group consisting of gastric adenocarcinoma, gastroesophageal junction (GEC) adenocarcinoma, esophageal adenocarcinoma, colorectal carcinoma (CRC), cholangiocarcinoma, gallbladder carcinoma, gastric cancer, lung cancer, biliary cancers, bladder cancer, esophageal cancer, melanoma, ovarian cancer, liver cancer, prostate cancer, pancreatic cancer, small intestine cancer, non-small cell lung cancer, head and neck cancer, uterine cancer, cervical cancer, brain cancer, and breast cancer.

~~17~~12. The usemethod of any one of claims 1-~~16~~11, wherein the HER2 positive cancer is gastric adenocarcinoma.

~~18~~13. The usemethod of any one of claims 1-~~17~~11, wherein the HER2 positive cancer is gastroesophageal junction (GEC) adenocarcinoma.

~~19~~14. The usemethod of any one of claims 1-~~18~~13, wherein the HER2 positive cancer is unresectable or metastatic.

~~20~~15. The usemethod of any one of claims 1-~~19~~14, wherein the subject has been previously treated with a HER2-directed antibody.

~~21~~16. The usemethod of any one of claims 1-~~20~~15, wherein the subject has not been previously treated with an anti-HER2 and/or an anti-EGFR tyrosine kinase inhibitor; and/or

~~22. The method of any one of claims 1-21, wherein the subject has not been previously treated with a HER2-directed antibody-drug conjugate; and/or an anthracycline.~~

~~23~~17. The usemethod of claim ~~21~~16, wherein the ~~wherein the~~ anti-HER2/EGFR tyrosine kinase inhibitor is selected from the group consisting of tucatinib, lapatinib, neratinib, or afatinib;.

~~24. The method of claim 22,~~ wherein the antibody-drug conjugate is selected from the group consisting of ado-trastuzumab (T-DM1) or trastuzumab deruxtecan (DS8201a); or

~~25. The method of any one of claims 1-24, wherein the subject has not been previously treated with an anthracycline.~~

~~26. The method of claim 25,~~ wherein the anthracycline is selected from the group consisting of doxorubicin, epirubicin, mitoxantrone, idarubicin, liposomal doxorubicin, and combinations thereof.

~~27~~¹⁸. The use method of any one of claims 1-~~26~~¹⁷, wherein the subject was previously treated with at least one anticancer therapy;

~~28. The method of claim 27, wherein the at least one anticancer therapy is~~ selected from the group consisting of trastuzumab, lapatinib, trastuzumab and a taxane, pertuzumab, and combinations thereof.

~~29~~¹⁹. The use method of ~~any one of claims 27 or 28~~ according to claim 18, wherein the subject is refractory to the at least one anticancer therapy; and/or

~~30. The method of any one of claims 27-29,~~ wherein the subject developed a brain metastasis during the previous treatment with the at least one anticancer therapy.

~~31~~²⁰. Use of tucatinib in the manufacture of a medicament for use in combinatorial therapy for ~~A method for~~ treating a HER2 positive cancer in a subject that has exhibited an adverse event after starting treatment with tucatinib in a combination ~~therapy comprising tucatinib, with~~ trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist at an initial dosage level, ~~comprising administering to wherein~~ the subject is to be administered at least one component of the tucatinib, trastuzumab, a taxane, and/or the vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist ~~combination therapy~~ at a reduced dosage level.

~~3221.~~ The ~~usemethod~~ of claim ~~31-20~~, wherein the taxane is selected from the group consisting of paclitaxel, docetaxel, cabazitaxel, larotaxel, BMS-184476, BMS-188797, BMS-275183, milataxel, ortaxel, TL-310, docosahexaenoic acid-paclitaxel (DHA-paclitaxel), nab paclitaxel, EndoTAG+paclitaxel, XRP9881, polymeric-micellar paclitaxel, RPR-109881A, a pharmaceutically acceptable salt or solvate thereof, and a combination thereof.

~~3322.~~ The ~~usemethod~~ of ~~any one of claims 31 or 32~~claim 21, wherein the taxane is paclitaxel-
and

~~34. The method of claim 33, wherein~~ the paclitaxel is to be administered to the subject at an initial dose of about 50 mg/m² to about 100 mg/m²; optionally

~~35. The method of any one of claims 33 or 34,~~ wherein the paclitaxel is to be administered to the subject at an initial dose of about 80 mg/m²; or

~~36. The method of any one of claims 33-35,~~ wherein the paclitaxel is to be administered to the subject at a reduced dose of about 50 mg/m² to about 75 mg/m²; or

~~37. The method of any one of claims 33-36~~ wherein the paclitaxel is to be administered to the subject at a reduced dose of about 70 mg/m²; or

~~38. The method of any one of claims 33-36,~~ wherein the paclitaxel is to be administered to the subject at a reduced dose of about 60 mg/m².

~~3923.~~ The ~~usemethod~~ of claim ~~31-38~~20 or 21, wherein the tucatinib is to be administered to the subject at an initial dose of about 150 mg to about 650 mg; optionally

~~40. The method of claim 31-39,~~ wherein the tucatinib is to be administered to the subject at an initial dose of about 300 mg; and/or

~~41. The method of any one of claims 31-40,~~ wherein the tucatinib is to be administered to the subject at a reduced dose of about 125 mg to about 275 mg.

~~42~~24. The use method of any one of claims ~~31-41~~21-23, wherein the VEGFR-2 antagonist is selected from the group consisting of bevacizumab, ramucirumab, aflibercept, cetuximab, panitumumab, regorafenib, sunitinib, sorafenib, pazopanib, vandetanib, axitinib, cediranib, vatalanib, motesanib, lucatinib, intedanib, semaxanib, apatinib, lenvatinib, carbozantinib, and a combination thereof.

~~43~~25. The use method of ~~any one of claims 31-42~~claim 24, wherein the VEGFR-2 antagonist is ramucirumab ~~and~~ and

~~44. The method of any one of claims 42 or 43, wherein~~ the ramucirumab is to be administered to the subject at an initial dose of about 8 mg/kg ~~, or~~ or

~~45. The method of any one of claims 42-44,~~ wherein the ramucirumab is to be administered to the subject at a reduced dose of about 6 mg/kg ~~, or~~ or

~~46. The method of any one of claims 42-44,~~ wherein the ramucirumab is administered to the subject at a reduced dose of about 5 mg/kg.

~~47~~26. The use of any one of claims 1-25, wherein A method of treating a HER2 positive cancer in a subject in need thereof, the method comprising:

~~(a) administering to the subject a therapeutically effective amount of a combination therapy comprising tucatinib, trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist; and~~

~~(b) administering the subject is to be further administered~~ an effective amount of an anti-diarrheal agent.

~~48. A method of reducing the severity or incidents of diarrhea, or preventing diarrhea in a subject having a HER2 positive cancer and being treated with an effective amount of a combination therapy comprising tucatinib, trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist, the method comprising administering an effective amount of an anti-diarrheal agent prophylactically.~~

~~49. A method of reducing the likelihood of a subject developing diarrhea, wherein the subject has a HER2 positive cancer and is being treated with an effective amount of a combination therapy comprising tucatinib, trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist the method comprising administering an effective amount of an anti-diarrheal agent prophylactically.~~

~~50. The method of any one of claims 47-49, wherein the combination therapy and the anti-diarrheal agent are administered concurrently.~~

~~51. The method of any one of claims 47-49, wherein the anti-diarrheal agent is administered prior to administration of the combination therapy.~~

~~52. The method of any one of claims 47-51, wherein the subject is exhibiting symptoms of diarrhea.~~

~~53. The method of any one of claims 47-51, wherein the subject is not exhibiting symptoms of diarrhea.~~