

SUMMARY

[0005] Provided herein are methods of treating cancer in a subject in need thereof, the method comprising 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.

[0005a] In one aspect, the present disclosure refers to 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, wherein said medicament is to be administered in combination with trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist.

[0006] Also provided herein are methods of treating cancer in a subject in need thereof, the method comprising: (a) identifying the subject as having a HER2 positive cancer; and (b) 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.

[0006a] In one aspect, the present disclosure refers to use of tucatinib in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject in need thereof, the use comprising: (a) identifying the subject as having a HER2 positive cancer; and (b) wherein the subject is to be administered a therapeutically effective amount of a combination therapy comprising the medicament, trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist.

[0007] In some embodimentexamples, the trastuzumab is administered to the subject at a dose of about 6 mg/kg. In some embodimentexamples, the trastuzumab is administered to the subject at a dose of about 4 mg/kg. In some embodimentexamples, the tucatinib is administered to the subject at a dose of about 150 mg to about 650 mg. In some embodimentexamples, the tucatinib is administered twice daily. In some embodimentexamples, the tucatinib is administered to the subject orally.

[0008] In some embodimentexamples, 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, Zenvatinib, carbozantinib, and a combination thereof. In some embodimentexamples, the VEGFR-2 antagonist is a monoclonal antibody selected from the group consisting of bevacizumab, ramucirumab, aflibercept, cetuximab, panitumumab, and combinations thereof. In some embodimentexamples, the VEGFR-2 antagonist is ramucirumab. In some embodimentexamples, the ramucirumab is administered to the subject at a dose of about 8 mg/kg.

[0009] In some embodimentexamples, 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. In some embodimentexamples, the taxane is selected from the group consisting of paclitaxel, docetaxel, and cabazitaxel. In some embodimentexamples, the taxane is paclitaxel. In some embodimentexample, the paclitaxel is administered to the subject at a dose of about

50 mg/m² to about 100 mg/m². In some [embodimentexamples](#), the paclitaxel is administered to the subject at a dose of about 80 mg/m².

[0010] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), 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, and brain cancer. In some [embodimentexamples](#), the HER2 positive cancer is gastric adenocarcinoma. In some [embodimentexamples](#), the HER2 positive cancer is gastroesophageal junction (GEC) adenocarcinoma. In some [embodimentexamples](#), the HER2 positive cancer is unresectable or metastatic.

[0011] In some [embodimentexamples](#), the subject has been previously treated with a HER2-directed antibody. In some [embodimentexamples](#), the subject has not been previously treated with an anti-HER2 and/or an anti-EGFR tyrosine kinase inhibitor. In some [embodimentexamples](#), the subject has not been previously treated with a HER2-directed antibody-drug conjugate. In some [embodimentexample](#), the wherein the anti-HER2/EGFR tyrosine kinase inhibitor is selected from the group consisting of tucatinib, lapatinib, neratinib, or afatinib. In some [embodimentexamples](#), the antibody-drug conjugate is selected from the group consisting of ado-trastuzumab (T-DM1) or trastuzumab deruxtecan (DS8201a).

[0012] In some [embodimentexamples](#), the subject has not been previously treated with an anthracycline. In some [embodimentexamples](#), the anthracycline is selected from the group consisting of doxorubicin, epirubicin, mitoxantrone, idarubicin, liposomal doxorubicin, and combinations thereof.

[0013] In some [embodimentexamples](#), the subject was previously treated with at least one anticancer therapy. In some [embodimentexamples](#), the at least one anticancer therapy is selected from the group consisting of trastuzumab, lapatinib, trastuzumab and a taxane, pertuzumab, and combinations thereof. In some [embodimentexamples](#), the subject is refractory to the at least one anticancer therapy. In some [embodimentexamples](#), the subject developed a brain metastasis during the previous treatment with the at least one anticancer therapy.

[0014] Provided herein are methods of treating a HER2 positive cancer in a subject that has exhibited an adverse event after starting treatment with a combination therapy comprising tucatinib, trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist at an initial dosage level, comprising administering to the subject at least one component of the combination therapy at a reduced dosage level.

[0014a] In one aspect, the present disclosure refers to use of tucatinib in the manufacture of a medicament for use in combinatorial therapy for treating a HER2 positive cancer in a subject that has exhibited an adverse event after starting treatment with tucatinib in combination with trastuzumab, a taxane, and a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist at an initial dosage level, 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 at a reduced dosage level.

[0015] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the taxane is paclitaxel.

[0016] In some [embodimentexamples](#), paclitaxel is administered to the subject at an initial dose of about 50 mg/m² to about 100 mg/m². In some [embodimentexamples](#), the paclitaxel is administered to the subject at an initial dose of about 80 mg/m². In some [embodimentexamples](#), the paclitaxel is administered to the subject at a reduced dose of about 50 mg/m² to about 75 mg/m². In some [embodimentexamples](#), the paclitaxel is administered to the subject at a reduced dose of about 70 mg/m². In some [embodimentexamples](#), the paclitaxel is administered to the subject at a reduced dose of about 60 mg/m².

[0017] In some [embodimentexamples](#), the tucatinib is administered to the subject at an initial dose of about 150 mg to about 650 mg. In some [embodimentexample](#), the tucatinib is administered to the subject at an initial dose of about 300 mg. In some [embodimentexamples](#), the tucatinib is administered to the subject at a reduced dose of about 125 mg to about 275 mg.

[0018] In some [embodimentexamples](#), 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. In some [embodimentexamples](#), the VEGFR-2 antagonist is ramucirumab. In some [embodimentexamples](#), the ramucirumab is administered to the subject at an initial dose of about 8 mg/kg. In some [embodimentexamples](#), the ramucirumab is administered to the subject at a reduced dose of about 6 mg/kg. In some [embodimentexamples](#), the ramucirumab is administered to the subject at a reduced dose of about 5 mg/kg.

[0019] Also provided herein are methods 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 an effective amount of an anti-diarrheal agent.

[0020] Also provided herein are methods 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.

[0021] Also provided herein are methods 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.

[0022] In some [embodimentexamples](#), the combination therapy and the anti-diarrheal agent are administered concurrently. In some [embodimentexamples](#), the anti-diarrheal agent is administered prior to administration of the combination therapy. In some [embodimentexamples](#), the subject is exhibiting symptoms of diarrhea. In some [embodimentexamples](#), the subject is not exhibiting symptoms of diarrhea.

DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 Shows a study schema including study visits, and the overall design of phase 2, and phase 3 associated with a phase 2/3 study of tucatinib in combination with trastuzumab, a taxane, and a VEGFR-2 antagonist for HER2+ positive cancers described herein in connection with Example 1.