

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

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

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

50 mg/m² to about 100 mg/m². In some examples, the paclitaxel is administered to the subject at a dose of about 80 mg/m².

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

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

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

[0013] In some examples, the subject was previously treated with at least one anticancer therapy. In some examples, 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 examples, the subject is refractory to the at least one anticancer therapy. In some examples, 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 examples, 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 examples, the taxane is paclitaxel.

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

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

[0018] In some examples, 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 examples, the VEGFR-2 antagonist is ramucirumab. In some examples, the ramucirumab is administered to the subject at an initial dose of about 8 mg/kg. In some examples, the ramucirumab is administered to the subject at a reduced dose of about 6 mg/kg. In some examples, 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 examples, the combination therapy and the anti-diarrheal agent are administered concurrently. In some examples, the anti-diarrheal agent is administered prior to administration of the combination therapy. In some examples, the subject is exhibiting symptoms of diarrhea. In some examples, 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.