METHODS OF TREATING HER2 POSITIVE CANCER WITH TUCATINIB IN COMBINATION WITH TRASTUZUMAB AND AN OXALIPLATIN-BASED CHEMOTHERAPY

BACKGROUND

[1] Encoded by the ERBB2 gene, human epidermal growth factor receptor 2 (HER2) is part of a family of 4 related receptor tyrosine kinases, which include HER1 (also known as epidermal growth factor receptor [EGFR]), HER2, HER3, and HER4. HER1-4 are single-pass transmembrane glycoprotein receptors containing an extracellular ligand binding region and an intracellular signaling domain. HER2 has no known ligand, but it is the preferred dimerization partner for the other HER family receptors. When overexpressed in tumors, HER2 forms ligand-independent homodimeric complexes that autophosphorylate. HER2 homo- or heterodimerization results in the activation of multiple signaling cascades, including the Ras/Raf/MEK/MAPK, PI3K/AKT, Src, and STAT pathways. These signaling pathways lead to cell proliferation, inhibition of apoptosis, and metastasis.

[2] The treatment and prevention of HER2 positive cancers represents an unmet need. Cancers that are characterized by the overexpression of HER2 (referred to as HER2 positive cancers) are often correlated with poor prognosis or are resistant to many standard therapies. Accordingly, there is a need for new therapies that are effective for the treatment of cancers such as HER2 positive cancers or metastatic HER2 positive cancers.

[3] 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

[4] Provided herein are methods of treating cancer in a subject in need thereof, the methods comprising identifying the subject as having a HER2 positive cancer; and administering to the subject a therapeutically effective amount of a combination therapy comprising tucatinib, trastuzumab, and an oxaliplatin-based chemotherapy. In one ~~aspect~~example, the present disclosure refers to a method of

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, trastuzumab and an oxaliplatin-based chemotherapy. In one aspect, the present disclosure refers to the use of tucatinib in the manufacture of a first medicament, use of trastuzumab in the manufacture of a second medicament, and use of an oxaliplatin-based chemotherapy in the manufacture of a third medicament, wherein a therapeutically effective amount of the first, second and third medicaments are to be used in combination therapy for treating a her2 positive cancer in a subject in need thereof.

[5] In some examples of any of the methods described herein, the oxaliplatin-based chemotherapy is oxaliplatin in combination with a compound selected from the group consisting of leucovorin (LV), fluorouracil, uracil-tegafur (UFT), irinotecan, and bevacizumab, or a combination thereof.

[6] In some examples of any of the methods described herein, the oxaliplatin-based chemotherapy is administered as a regimen selected from the group consisting of FOLFOX4, mFOLFOX4, FOLFOX6, mFOLFOX6, FOLFOX7, mFOLFOX7, FOLFOXIRI, bFOL, PVIFOX, IROX, FUOX, FuFOX, CapeOx, XELOX, and CAPOX.

[7] In some examples of any of the methods described herein, the oxaliplatin-based chemotherapy comprises administering oxaliplatin, leucovorin, and fluorouracil by an mFOLFOX7 regimen.

[8] In some examples of any of the methods described herein, the HER2 positive cancer is selected from the group consisting of gastric adenocarcinoma, gastroesophageal junction (GEJ) 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.

[9] In some examples of any of the methods described herein, the HER2 positive cancer is gastric adenocarcinoma, gastroesophageal junction (GEJ) adenocarcinoma, esophageal adenocarcinoma, colorectal carcinoma (CRC), cholangiocarcinoma, or gallbladder carcinoma. In some examples, the HER2 positive cancer is unresectable or metastatic.

[10] In some examples of any of the methods described herein, the subject has not been previously treated with a cancer therapy. In some examples, of any of the methods described herein, the subject has not been previously treated with tucatinib. In some examples of any of the methods described herein, the subject has not been previously treated with trastuzumab. In

some examples of any of the methods described herein, the subject has not been previously treated with an oxaliplatin-based chemotherapy.

[11] In some examples of any of the methods described herein, the subject is a candidate to receive an oxaliplatin-based chemotherapy.

[12] In some examples of any of the methods described herein, the subject was previously treated or is a caudate to receive an anticancer therapy. In some examples of any of the methods described herein, the subject was previously treated or is currently being treated with an oxaliplatin-based chemotherapy. In some examples of any of the methods described herein, the subject was previously treated with at least one anticancer therapy. In some examples of any of the methods described herein, the least one anticancer therapy is an anti-HER2 antibody or anti-HER2 antibody-drug conjugate. In some examples of any of the methods described herein, the at least one previous anticancer therapy is selected from the group consisting of trastuzumab, trastuzumab and a taxane, pertuzumab, ado-trastuzumab (T-DM1), and combinations thereof.

[13] In some examples of any of the methods described herein, the subject is refractory to the previous anticancer therapy. In some examples of any of the methods described herein, the subject developed a brain metastasis during the previous anticancer therapy.

[14] In some examples of any of the methods described herein, the subject has not been treated with another anticancer therapy within the past 12 months.

[15] In some examples of any of the methods described herein, the tucatinib is administered to the subject at a dose of about 100 mg to about 1000 mg. In some examples of any of the methods described herein, the tucatinib is administered twice daily. In some examples of any of the methods described herein, the tucatinib is administered to the subject orally. In some examples of any of the methods described herein, the trastuzumab is administered to the subject at a dose of about 6 mg/kg. In some examples of any of the methods described herein, the trastuzumab is administered to the subject at a dose of about 4 mg/kg.

[16] In one ~~aspect~~example, the present disclosure refers to a method for treating a HER2 positive cancer in a subject that has exhibited an adverse event after starting treatment with a combination therapy comprising

tucatinib, trastuzumab, and an oxaliplatin-based chemotherapy at an initial dosage level, comprising administering to the subject the at least one component of the combination therapy at a reduced dosage level. In one aspect, the present disclosure refers to the use of tucatinib in the manufacture of a first medicament, use of trastuzumab in the manufacture of a second medicament, and use of an oxaliplatin-based chemotherapy in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used in combination therapy for treating a her2 positive cancer in a subject that has exhibited an adverse event after starting treatment with a combination therapy comprising tucatinib, trastuzumab, and an oxaliplatin-based chemotherapy at an initial dosage level, wherein at least one of the medicaments is to be administered at a reduced dosage level.

[17] In some examples of any of the methods described herein, the tucatinib is administered to the subject at a dose of about 100 mg to about 1000 mg. In some examples of any of the methods described herein, the trastuzumab is administered to the subject at a dose of about 6 mg/kg. In some examples of any of the methods described herein, the trastuzumab is administered to the subject at a dose of about 4 mg/kg.

[18] Also provided herein are kits for treating or ameliorating the effects of a HER2 positive cancer in a subject, the kit comprising tucatinib, trastuzumab, and an oxaliplatin-based chemotherapy.

[19] Also provided herein are methods of treating a HER2 positive cancer in a subject in need thereof, the methods comprising administering to the subject a therapeutically effective amount of a combination therapy comprising tucatinib, trastuzumab, and an oxaliplatin-based chemotherapy, and administering an effective amount of an anti-diarrheal agent.

[20] 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, and an oxaliplatin-based chemotherapy, the methods comprising administering an effective amount of an anti-diarrheal agent prophylactically.

[21] 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, and an oxaliplatin-based chemotherapy the method comprising administering an effective amount of an anti-diarrheal agent prophylactically.

[22] In some examples of any of the methods described herein, the combination therapy and the anti-diarrheal agent are administered concurrently. In some examples of any of the methods described herein, the anti-diarrheal agent is administered prior to administration of the combination therapy. In some examples of any of the methods described herein, the subject

CLAIMS

1. Use of tucatinib in the manufacture of a first medicament, use of trastuzumab in the manufacture of a second medicament, and use of an oxaliplatin-based chemotherapy in the manufacture of a third medicament, wherein a therapeutically effective amount of the first, second and third medicaments are to be used in combination therapy for ~~A method of~~ 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, trastuzumab and an oxaliplatin-based chemotherapy~~.

2. The ~~method~~ use of claim 1, wherein the oxaliplatin-based chemotherapy is oxaliplatin in combination with a compound selected from the group consisting of leucovorin (LV), fluorouracil, uracil-tegafur (UFT), irinotecan, and bevacizumab, or a combination thereof.

3. The ~~method~~ use of any one of claims 1 or 2 wherein the oxaliplatin-based chemotherapy is to be administered as a regimen selected from the group consisting of FOLFOX4, mFOLFOX4, FOLFOX6, mFOLFOX6, mFOLFOX7, FOLFOXIRI, bFOL, PVIFOX, IROX, FUOX, FuFOX, CapeOx, XELOX, and CAPOX.

4. The ~~method~~ use of any one of claims 1-3, wherein the oxaliplatin-based chemotherapy comprises oxaliplatin, leucovorin, and fluorouracil administered as an mFOLFOX7 regimen.

5. The ~~method~~ use of any one of claims 1-4, wherein the HER2 positive cancer is selected from the group consisting of gastric adenocarcinoma, gastroesophageal junction (GEJ) 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

6. The ~~method~~ use of any one of claims 1-5, wherein the HER2 positive cancer is gastric adenocarcinoma.

7. The ~~method~~ use of any one of claims 1-5, wherein the HER2 positive cancer is gastroesophageal junction (GEJ) adenocarcinoma.

8. The ~~method~~ use of any one of claims 1-5, wherein the HER2 positive cancer is esophageal adenocarcinoma.

9. The ~~method~~ use of any one of claims 1-5, wherein the HER2 positive cancer is colorectal carcinoma (CRC).

10. The ~~method~~ use of any one of claims 1-5, wherein the HER2 positive cancer is cholangiocarcinoma.

11. The ~~method~~ use of any one of claims 1-5, wherein the HER2 positive cancer is gallbladder carcinoma.

12. The ~~method~~ use of any one of claims 1-11, wherein the HER2 positive cancer is unresectable or metastatic.

13. The ~~method~~ use of any one of claims 1-12, wherein the subject was previously treated with at least one anticancer therapy, and wherein the subject is refractory to the at least one anticancer therapy, and/or wherein the subject developed a brain metastasis during the previous treatment with the at least one anticancer therapy.

14. The ~~method~~ use of any one of claims 1-13, wherein the tucatinib is to be administered to the subject at a dose of about 100 mg to about 1000 mg.

15. The ~~method~~ use of any one of claims 1-14, wherein the tucatinib is to be administered twice daily.

16. The ~~method~~ use of any one of claims 1-15, wherein the trastuzumab is to be administered to the subject at a dose of about 6 mg/kg, or wherein the trastuzumab is to be administered to the subject at a dose of about 4 mg/kg.

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

18. The ~~method~~ use of claim 17, wherein the tucatinib is to be administered to the subject at a dose of about 100 mg to about 1000 mg.

19. The ~~method~~ use of any one of claims 17 or 18, wherein the trastuzumab is to be administered to the subject at a dose of about 6 mg/kg, or wherein the trastuzumab is to be administered to the subject at a dose of about 4 mg/kg.

20. The ~~method~~ use of any one of claims 1-19, ~~further comprising administering to~~wherein the subject is to be administered an effective amount of an anti-diarrheal agent.