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, 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.

[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, 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.

[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

is exhibiting symptoms of diarrhea. In some examples of any of the methods described herein, the subject is not exhibiting symptoms of diarrhea.

DESCRIPTION OF THE DRAWINGS

[23] FIG. 1 Shows a dose escalation cohort associated with a Phase 1b, dose escalation study of tucatinib in combination with trastuzumab and an oxaliplatin-based chemotherapy for HER2+ positive cancers described herein in connection with Example 1.

[24] FIG. 2 provides the amino acid sequence of the heavy (SEQ. ID NO. 1) and light chains (SEQ. ID NO. 2) of trastuzumab and the light chain variable domain (SEQ. ID NO. 3) and the heavy chain variable domain (SEQ. ID NO. 4).

[25] FIGS. 3A-3C show that a combination of tucatinib and trastuzumab was active in HER2 amplified colorectal cancer (CRC) patient-derived xenograft (PDX) models. Data are shown as group mean +/- S.E.M. FIG. 3A shows the effects of tucatinib and trastuzumab, alone and in combination, on tumor growth in a CTG-0121 CRC PDX model. FIG. 3B shows the effects of tucatinib and trastuzumab, alone and in combination, on tumor growth in a CTG-0784 CRC PDX model. FIG. 3C shows the effects of tucatinib and trastuzumab, alone and in combination, on tumor growth in a CTG-0383 CRC PDX model.

[26] FIGS. 4A and 4B show that a combination of tucatinib and trastuzumab was active in HER2 amplified esophageal cancer patient-derived xenograft (PDX) models. Data are shown as group mean +/- S.E.M. FIG. 4A shows the effects of tucatinib and trastuzumab, alone and in combination, on tumor growth in a CTG-0137 esophageal cancer PDX model. FIG. 4B shows the effects of tucatinib and trastuzumab, alone and in combination, on tumor growth in a CTG-0138 esophageal cancer PDX model.

[27] FIGS. 5A-5C show that a combination of tucatinib and trastuzumab was active in HER2 positive gastric cancer patient-derived xenograft (PDX) models. Data are shown as group mean +/- S.D. FIG. 5A shows the effects of tucatinib and trastuzumab, alone and in combination, on tumor growth in a GXA 3038 gastric cancer PDX model. FIG. 5B shows the effects of tucatinib and trastuzumab, alone and in combination, on tumor growth in a GXA 3039 gastric cancer PDX

CLAIMS

1. 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 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 of any one of claims 1 or 2 wherein the oxaliplatin-based chemotherapy is 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 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 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 of any one of claims 1-5, wherein the HER2 positive cancer is gastric adenocarcinoma.

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

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

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

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

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

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

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

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

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

17. 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.

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

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

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