[0005] The MOUNTAINEER clinical trial (ClinicalTrials.gov Identifier #NCT03043313), is examining the efficacy of a combination of tucatinib and trastuzumab for the treatment of patients with HER2 positive metastatic CRC.

[0006] 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. The present invention satisfies this need, and provides other advantages as well.

SUMMARY

[0007] In one aspect, the present disclosure refers to use of a combination therapy in the manufacture of a medicament for treating or ameliorating the effects of a HER2 positive cancer in a subject, wherein the combination therapy comprises an anti-HER2 antibody and tucatinib. In another aspect, the present disclosure refers to use of a combination therapy comprising an anti-HER2 antibody and tucatinib in the manufacture of medicament for treating a HER2 positive cancer in a subject that has exhibited an adverse event after starting treatment with the combination therapy at an initial dosage level, wherein the medicament is to be administered at a reduced dosage level. In some examples, the present disclosure provides a method for treating or ameliorating the effects of a HER2 positive cancer in a subject, the method comprising administering an anti-HER2 antibody in combination with tucatinib and a chemotherapeutic agent to thereby treat the HER2 positive cancer. In some examples, the cancer is selected from the group consisting of colorectal cancer, esophageal cancer, gastric cancer, cholangiocarcinoma, non-small cell lung cancer, bladder cancer, biliary cancer, breast cancer, and a combination thereof. In some examples, the cancer is breast cancer. In some examples, the cancer is a metastatic cancer. In some examples, the cancer is an unresectable, locally advanced cancer.

[0008] In some examples, the anti-HER2 antibody is a member selected from the group consisting of trastuzumab, pertuzumab, ado-trastuzumab emtansine, margetuximab, and a combination thereof. In some instances, the anti-HER2 antibody is trastuzumab. In some instances, the anti-HER2 antibody is a combination of trastuzumab and pertuzumab. In some examples, the administration of the anti-HER2 antibody is before, during, or after the administration of tucatinib.

[0009] In some examples, the cancer comprises a cell that has a wild-type *KRAS* exon 2 genotype. In some examples, the cancer comprises a cell that has a wild-type *NRAS* genotype. In some examples, the cancer comprises a cell that has a wild-type *BRAF* genotype. In yet some examples, the subject has a cancer that is refractory to a standard of care which includes cetuximab or panitumumab.

[0010] In some examples, treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%. In some instances, treating the subject results in a TGI index of about 100%. In some examples, the combination of the anti-HER2 antibody and

tucatinib is synergistic. In some examples, treating the subject results in a TGI index that is greater than the TGI index observed when using an anti-HER2 antibody or tucatinib alone.

[0011] In some examples, a dose of tucatinib is about 3 to 7 mg per kg of the subject's body weight twice daily. In some examples, a dose of tucatinib is about 300 mg twice per day. In some examples, a dose of the anti-HER2 antibody is about 6 mg to 8 mg per kg of the subject's body weight once every three weeks. In some examples, a dose of the anti-HER2 antibody is about 600 mg once every three weeks. In some examples, the tucatinib or the anti-HER2 antibody is administered orally, intravenously, or subcutaneously.

[0012] In some examples, the use or method further comprises administering a chemotherapeutic agent (*e.g.*, an antimetabolite, such as capecitabine). In some examples, the antimetabolite is a member selected from the group consisting of capecitabine, carmofur, doxidluridine, fluorouracil, tegafur, and a combination thereof. In some examples, the antimetabolite is capecitabine. In some examples, a dose of capecitabine is about 1,000 mg per m^2 of the subject's body surface area twice per day. In some examples, the chemotherapeutic agent is administered orally. In some examples, the capecitabine is administered in 150 mg or 500 mg tablets.

[0013] In other examples, the present disclosure provides a pharmaceutical composition comprising an anti-HER2 antibody, tucatinib, and a pharmaceutically acceptable carrier. In some examples, the anti-HER2 antibody is a member selected from the group consisting of trastuzumab, pertuzumab, ado-trastuzumab emtansine, margetuximab, and a combination thereof. In some instances, the anti-HER2 antibody is trastuzumab. In some instances, the anti-HER2 antibody is a combination of trastuzumab and pertuzumab. In some examples, the pharmaceutical composition further comprises a chemotherapeutic agent. In one aspect therefore, the present disclosure refers to a pharmaceutical composition comprising an anti-HER2 antibody, tucatinib, a chemotherapeutic agent, and a pharmaceutically acceptable carrier. In some examples, the chemotherapeutic agent is an antimetabolite. In some examples, the antimetabolite is capecitabine.

[0014] In still other aspects, the present disclosure provides a kit for treating or ameliorating the effects of a HER2 positive cancer in a subject, the kit comprising a pharmaceutical composition of the present disclosure. In some examples, the kit further comprises instructions for use. In some examples, the kit comprises one or more reagents.

[0015] Other objects, features, and advantages of the present disclosure will be apparent to one of skill in the art from the following detailed description and figures.

WHAT IS CLAIMED IS:

1. Use of a combination therapy in the manufacture of a medicament for treating or ameliorating the effects of a HER2 positive cancer in a subject, wherein the combination therapy comprises an anti-HER2 antibody and tucatinib.

2. The use of claim 1, wherein the combination therapy further comprises a chemotherapeutic agent.

3. The use of claim 2, wherein the chemotherapeutic agent is an antimetabolite.

4. The use of claim 3, wherein the antimetabolite is a member selected from the group consisting of capecitabine, carmofur, doxidluridine, fluorouracil, tegafur, and a combination thereof.

5. The use of claim 4, wherein the antimetabolite is capecitabine.

6. The use of any one of claims 1-5, wherein the cancer is selected from the group consisting of colorectal cancer, esophageal cancer, gastric cancer, cholangiocarcinoma, non-small cell lung cancer, bladder cancer, biliary cancer, breast cancer, and a combination thereof.

7. The use of any one of claims 1-6, wherein the cancer is an unresectable locally advanced cancer or a metastatic cancer.

8. The use of any one of claims 1-7, wherein the cancer is breast cancer.

9. The use of any one of claims 1-8, wherein the subject had prior treatment with trastuzumab, pertuzumab, and T-DM1.

10. The use of any one of claims 1-8, wherein the anti-HER2 antibody is a member selected from the group consisting of trastuzumab, pertuzumab, ado-trastuzumab emtansine, margetuximab, and a combination thereof.

11. The use of any one of claims 1-10, wherein the anti-HER2 antibody is trastuzumab.

12. The use of any one of claims 1-10, wherein the anti-HER2 antibody is a combination of trastuzumab and pertuzumab.

13. The use of any one of claims 10-12, wherein the antimetabolite is capecitabine

14. The use of any one of claims 1-13, wherein the anti-HER2 antibody is to be administered before, during, or after the administration of tucatinib.

15. The use of any one of claims 1-14, wherein the cancer comprises a cell that has a wild-type *KRAS* exon 2 genotype.

16. The use of any one of claims 1-15, wherein the cancer comprises a cell that has a wild-type *NRAS* genotype.

17. The use of any one of claims 1-16, wherein the cancer comprises a cell that has a wild-type *BRAF* genotype.

18. The use of any one of claims 1-17, wherein the subject has a cancer which is relapsed or refractory to a standard of care.

19. The use of any one of claims 1-18, wherein treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%.

20. The use of any one of claims 1-19, wherein treating the subject results in a TGI index of about 100%.

21. The use of any one of claims 1-20, wherein the combination of the anti-HER2 antibody and tucatinib is synergistic.

22. The use of any one of claims 1-21, wherein treating the subject results in a TGI index that is greater than the TGI index observed when using an anti-HER2 antibody or tucatinib alone.

23. The use of any one of claims 1-22, wherein a dose of tucatinib is about 3 to 7 mg per kg of the subject's body weight twice daily.

24. The use of any one of claims 1-22, wherein a dose of tucatinib is about 300 mg twice per day.

25. The use of any one of claims 1-24, wherein a dose of the anti-HER2 antibody is about 6 mg to 8 mg per kg of the subject's body weight once every three weeks.

26. The use of any one of claims 1-24, wherein a dose of the anti-HER2 antibody is about 600 mg once every three weeks.

27. The use of any one of claims 1-26, wherein the tucatinib or the anti-HER2 antibody is to be administered orally.

28. The use of any one of claims 1-27, wherein the antimetabolite is to be administered orally.

29. The use of claim 28, wherein a dose of the antimetabolite is about 1,000 mg per m^2 of the subject's body surface area twice per day.

30. The use of claim 28 or 29, wherein the anti-HER2 antibody is to be administered intravenously or subcutaneously.

31. The use of any one of claims 1-30, wherein one or more therapeutic effects in the subject is improved after administration of the combination therapy relative to a baseline.

32. The use of claim 31, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.

33. The use of claim 32, wherein the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least

about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of the combination therapy.

34. The use of claim 32, wherein the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%.

35. The use of claim 32, wherein the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the combination therapy.

36. The use of claim 32, wherein the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the combination therapy.

37. The use of claim 32, wherein the duration of response to the antibody-drug conjugate is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the combination therapy.

38. The use of any one of claims 1-37, wherein the subject has one or more adverse events and is to be further administered an additional therapeutic agent to eliminate or reduce the severity of the one or more adverse events.

39. The use of any one of claims 1-38, wherein the subject is at risk of developing one or more adverse events and is to be further administered an additional therapeutic agent to prevent or reduce the severity of the one or more adverse events.

40. The use of claim 38 or 39, wherein the one or more adverse events is a grade 2 or greater adverse event.

41. The use of claim 40, wherein the one or more adverse events is a grade 3 or greater adverse event.

42. The use of any one of claims 38-41, wherein the one or more adverse events is a serious adverse event.

43. The use of any one of claims 1-42, wherein the subject is a human.

44. Use of a combination therapy comprising an anti-HER2 antibody and tucatinib in the manufacture of medicament for treating a HER2 positive cancer in a subject that has exhibited an adverse event after starting treatment with the combination therapy at an initial dosage level, wherein the medicament is to be administered at a reduced dosage level.

45. The use of claim 44, wherein the combination therapy further comprises a chemotherapeutic agent.

46. The use of claim 45, wherein the chemotherapeutic agent is an antimetabolite.

47. The use of claim 46, wherein the antimetabolite is a member selected from the group consisting of capecitabine, carmofur, doxidluridine, fluorouracil, tegafur, and a combination thereof.

48. The use of claim 47, wherein the antimetabolite is capecitabine.

49. The use of any one of claims 44-48, wherein the one or more adverse events is a grade 2 or greater adverse event.

50. The use of claim 49, wherein the one or more adverse events is a grade 3 or greater adverse event.

51. The use of any one of claims 44-50, wherein the adverse event is hepatotoxicity.

52. The use of any one of claims 44-50, wherein the adverse event is left ventricular dysfunction.

53. The use of any one of claims 44-50, wherein the adverse event is prolongation of the QTc interval.

54. The use of any one of claims 44-53, wherein the cancer is an unresectable locally advanced cancer or a metastatic cancer.

55. The use of any one of claims 44-54, wherein the cancer is breast cancer.

56. The use of any one of claims 44-55, wherein the subject had prior treatment with trastuzumab, pertuzumab, and T-DM1.

57. The use of any one of claims 44-56, wherein the initial dosage level of tucatinib is about 300 mg twice daily.

58. The use of any one of claims 44-57, wherein the reduced dosage level of tucatinib is about 250 mg twice daily.

59. The use of any one of claims 44-57, wherein the reduced dosage level of tucatinib is about 200 mg twice daily.

60. The use of any one of claims 44-57, wherein the reduced dosage level of tucatinib is about 150 mg twice daily.

61. A pharmaceutical composition comprising an anti-HER2 antibody, tucatinib, a chemotherapeutic agent, and a pharmaceutically acceptable carrier.

62. The pharmaceutical composition of claim 61, wherein the anti-HER2 antibody is a member selected from the group consisting of trastuzumab, pertuzumab, ado-trastuzumab emtansine, margetuximab, and a combination thereof.

63. The pharmaceutical composition of claim 61 or 62, wherein the anti-HER2 antibody is trastuzumab.

64. The pharmaceutical composition of claim 61 or 62, wherein the anti-HER2 antibody is a combination of trastuzumab and pertuzumab.

65. The pharmaceutical composition of any one of claims 61-64, wherein the chemotherapeutic agent is capecitabine.

66. A kit for treating or ameliorating the effects of a HER2 positive cancer in a subject, the kit comprising the pharmaceutical composition of any one of claims 61-65.

67. The kit of claim 66, further comprising instructions for use.

68. The kit of claim 66 or 67, further comprising one or more reagents.