such as whole brain radiation therapy (WBRT), stereotactic radiation (SRS), or surgery. Patients may also receive chemotherapy alone, or capecitabine and either lapatinib or trastuzumab, although brain response rates are generally modest. The development of HER2-targeted systemic therapies with clinical benefit in both brain and non-CNS sites of disease could lead to improved clinical outcomes, both by improving overall PFS and OS as well as by avoiding or delaying the use of radiation therapy and its associated toxicities, including neurocognitive impairment.

[7] Accordingly, there is a need for new therapies that are effective for the treatment of patients with HER2-positive breast cancer (*e.g.,* patients with unresectable, locally advanced, or metastatic HER2-positive breast cancer, including patients with brain metastases).

[8] 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

[8a] In one aspect, the present disclosure refers to use of tucatinib in the manufacture of a medicament for use in combinatorial therapy for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein said medicament is to be administered with capecitabine and trastuzumab, wherein following administration of the combinatorial therapy, the subject exhibits progression-free survival of at least 6 months or at least 7.5 months, or the subject exhibits an overall survival of at least eighteen months.

[8b] In one aspect, the present disclosure refers to use of tucatinib in the manufacture of a first medicament, use of capecitabine in the manufacture of a second medicament, and use of trastuzumab in the manufacture of a third medicament, wherein the first, second, and third medicaments are to be used in combination therapy to treat or ameliorate a HER2 positive breast cancer in a subject in need thereof, wherein said combination therapy comprises the separate, sequential or simultaneous administration of said first, second, and third medicaments, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months or at least 7.5 months, or the subject exhibits an overall survival of at least eighteen months.

[9] Provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 7.5 months following administration of the combination therapy. For example, wherein the subject exhibits progression-free survival of at least eight months, at least nine months, or at least ten months following administration of the combination therapy.

[10] Also provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy, the subject exhibits an overall survival of at least eighteen months following administration of the combination therapy. For example, wherein the subject exhibits an overall survival of at least nineteen months, at least twenty-two months, at least twenty-six months, or at least thirty months following administration of the combination therapy.

[11] In some of the ~~embodiment~~examples as provided herein, the subject has a brain metastasis.

[12] Accordingly, provided herein are methods of treating or ameliorating brain metastasis in a subject having HER2 positive breast cancer, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab. In some ~~embodiment~~examples, the time to additional intervention (e.g., radiation, surgery, or a combination thereof) for treatment of the brain metastasis in the subject has been increased. In some ~~embodiment~~examples, the need for additional intervention (e.g., radiation, surgery, or a combination thereof) for treatment of the brain metastasis in the subject has been prevented. In some ~~embodiment~~examples, regression of an existing brain metastasis in the subject has been promoted. In some ~~embodiment~~examples, the size of an existing brain metastasis in the subject has been reduced.

[13] This disclosure also provides methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has brain metastasis, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months following administration of the combination therapy. For example, the subject can exhibit progression-free survival of at least seven months or at least nine months following administration of the combination therapy.

[14] Methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof are also provided, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein the subject exhibits a greater than 40% reduction in the risk of disease progression or death as compared to a subject administered trastuzumab and capecitabine alone. For example, the subject can exhibit a greater than 45% reduction in the risk of disease progression or death as compared to a subject administered trastuzumab and capecitabine alone.

[15] Provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the methods comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein the subject exhibits a greater than 30% reduction in the risk of death as compared to a subject administered trastuzumab and capecitabine alone.

[16] Also provided herein are methods for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the methods

anti-diarrheal agent prophylactically. This disclosure also provides methods of reducing the likelihood of a subject developing diarrhea, wherein the subject has a HER2 positive breast cancer and is being treated with an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, the method comprising administering an effective amount of an anti-diarrheal agent prophylactically. In some such methods, the combination therapy and the anti-diarrheal agent can be administered concurrently. In some such methods, the anti-diarrheal agent is administered prior to administration of the combination therapy. In some ~~embodiment~~examples, the subject is exhibiting symptoms of diarrhea. In other ~~embodiment~~examples, the subject is not exhibiting symptoms of diarrhea.

DETAILED DESCRIPTION

I. Definitions

[25] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[26] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure. For purposes of the present disclosure, the following terms are defined.

[27] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

CLAIMS

1. ~~A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising~~Use of tucatinib in the manufacture of a medicament for use in combinatorial therapy for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein said medicament is to be administered with capecitabine~~,~~ and trastuzumab, wherein following administration of the combinatorial~~combination~~ therapy, the subject exhibits progression-free survival of at least 6 months or at least 7.5 months, or the subject exhibits an overall survival of at least eighteen months~~following administration of the combination therapy~~.

2. The use according to~~method of~~ claim 1, wherein the subject exhibits progression-free survival of at least seven months, at least eight months, at least nine months, or at least ten months, following administration of the combination therapy, or wherein the subject exhibits an overall survival of at least nineteen months, at least twenty-two months, at least twenty-six months, or at least thirty months, following administration of the combination therapy.

~~3. The method of any one of claims 1 or 2, wherein the subject exhibits progression free survival of at least nine months following administration of the combination therapy.~~

~~4. The method of any one of claims 1-3, wherein the subject exhibits progression-free survival of at least ten months following administration of the combination therapy.~~

~~5. The method of any one of claims 1-4, wherein the subject has a brain metastasis.~~

~~6. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy, the subject exhibits an overall survival of at least eighteen months following administration of the combination therapy.~~

~~7. The method of claim 6, wherein the subject exhibits an overall survival of at least nineteen months following administration of the combination therapy.~~

~~8. The method of any one of claims 6 or 7, wherein the subject exhibits an overall survival of at least twenty-two months following administration of the combination therapy.~~

9. The method of any one of claims 6-8, wherein the subject exhibits an overall survival of at least twenty-six months following administration of the combination therapy.

10. The method of any one of claims 6-9, wherein the subject exhibits an overall survival of at least thirty months following administration of the combination therapy.

11. The method of any one of claims 6-10, wherein the subject has a brain metastasis.

12. A method of treating or ameliorating brain metastasis in a subject having HER2 positive breast cancer, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab.

13. The method of claim 12, wherein the time to additional intervention for treatment of the brain metastasis in the subject has been increased.

14. The method of any one of claims 12 or 13, wherein the need for additional intervention for treatment of the brain metastasis in the subject has been prevented.

15. The method of claim 14, wherein the additional intervention is selected from the group consisting of radiation, surgery, and a combination thereof.

16. The method of any one of claims 12-15, wherein regression of an existing brain metastasis in the subject has been promoted.

17. The method of any one of claims 12-16, wherein the size of an existing brain metastasis in the subject has been reduced.

18. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has brain metastasis, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months following administration of the combination therapy.

19. The method of claim 18, wherein the subject exhibits progression-free survival of at least seven months following administration of the combination therapy.

20. The method of any one of claims 18 or 19, wherein the subject exhibits progression-free survival of at least nine months following administration of the combination therapy.

21. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein the

~~subject exhibits a greater than 40% reduction in the risk of disease progression or death as compared to a subject administered trastuzumab and capecitabine alone.~~

~~22. The method of claim 21, wherein the subject administered the combination therapy comprising tucatinib, capecitabine, and trastuzumab exhibits a greater than 45% reduction in the risk of disease progression or death as compared to a subject administered trastuzumab and capecitabine alone.~~

~~23. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein the subject exhibits a greater than 30% reduction in the risk of death as compared to a subject administered trastuzumab and capecitabine alone.~~

~~24. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein the subject exhibits a greater than 50% reduction in the risk of disease progression or death as compared to a subject administered trastuzumab and capecitabine alone.~~

~~25. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy for nine months, the subject has an estimated progression-free survival rate of greater than 40%.~~

~~26. The method of claim 25, wherein the subject has an estimated progression-free survival rate of greater than 45%.~~

~~27. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 25%.~~

~~28. The method of claim 27, wherein the subject has an estimated progression-free survival rate of greater than 30%.~~

29. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy for fifteen months, the subject has an estimated progression free survival rate of greater than 20%.

30. The method of claim 29, wherein the subject has an estimated progression free survival rate of greater than 25%.

31. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy for twenty-four months, the subject has an estimated overall survival rate of greater than 35%.

32. The method of claim 31, wherein the subject has an estimated overall survival rate of greater than 40%.

33. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy for thirty months, the subject has an estimated overall survival rate of greater than 30%.

34. The method of claim 33, wherein the subject has an estimated overall survival rate of greater than 40%.

35. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy for nine months, the subject has an estimated progression free survival rate of greater than 30%.

36. The method of claim 35, wherein the subject has an estimated progression free survival rate of greater than 40%.

37. A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof, wherein the subject has a brain metastasis, the method comprising administering

~~to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, wherein following administration of the combination therapy for twelve months, the subject has an estimated progression-free survival rate of greater than 15%.~~

~~38. The method of claim 37, wherein the subject has an estimated progression-free survival rate of greater than 20%.~~

~~39.~~3. The use according to claim 1 or 2~~A method for treating or ameliorating a HER2 positive breast cancer in a subject in need thereof~~, ~~the method comprising administering to the subject an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab and~~ wherein an effective amount of an anti-diarrheal agent is to be further administered to the subject.

4. Use of tucatinib in the manufacture of a first medicament, use of capecitabine in the manufacture of a second medicament, and use of trastuzumab in the manufacture of a third medicament, wherein the first, second, and third medicaments are to be used in combination therapy to treat or ameliorate a HER2 positive breast cancer in a subject in need thereof, wherein said combination therapy comprises the separate, sequential or simultaneous administration of said first, second, and third medicaments, wherein following administration of the combination therapy, the subject exhibits progression-free survival of at least 6 months or at least 7.5 months, or the subject exhibits an overall survival of at least eighteen months.

~~40. The method of claim 39, wherein the combination therapy and the anti-diarrheal agent are administered concurrently.~~

~~41. The method of claim 39, wherein the anti-diarrheal agent is administered prior to administration of the combination therapy.~~

~~42. The method of claim 39-41, wherein the subject is exhibiting symptoms of diarrhea.~~

~~43. The method of claim 39-41, wherein the subject is not exhibiting symptoms of diarrhea.~~

~~44. A method of reducing the severity or incidents of diarrhea, or preventing diarrhea in a subject having a HER2 positive breast cancer and being treated with an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, the method comprising administering an effective amount of an anti-diarrheal agent prophylactically.~~

~~45. The method of claim 44, wherein the combination therapy and the anti-diarrheal agent are administered concurrently.~~

~~46. The method of claim 44, wherein the anti-diarrheal agent is administered prior to administration of the combination therapy.~~

~~47. A method of reducing the likelihood of a subject developing diarrhea, wherein the subject has a HER2 positive breast cancer and is being treated with an effective amount of a combination therapy comprising tucatinib, capecitabine, and trastuzumab, the method comprising administering an effective amount of an anti-diarrheal agent prophylactically.~~

~~48. The method of claim 47, wherein the combination therapy and the anti-diarrheal agent are administered concurrently.~~

~~49. The method of claim 47, wherein the anti-diarrheal agent is administered prior to administration of the combination therapy.~~

~~50.~~5. The ~~method of~~use according to any one of claims 1-4~~9~~, wherein the tucatinib is to be administered to the subject at a dose of about 150 mg to about 650 mg or at a dose of about 300 mg.

~~51. The method of claim 50, wherein the tucatinib is administered to the subject at a dose of about 300 mg.~~

~~52.~~6. The ~~method of claim 50 or 51~~use according to claim 5, wherein the tucatinib is to be administered once or twice per day.

~~53.~~7. The use according to claim 6~~method of claim 52~~, wherein the tucatinib is to be administered to the subject at a dose of about 300 mg twice per day.

~~54. The method of any one of claims 1-53, wherein the tucatinib is administered to the subject orally.~~

~~55.~~8. The use according to any one of claims 1-7~~method of any one of claims 1-53~~, wherein the capecitabine is to be administered to the subject at a dose of about 500 mg/m^2 to about 1500 mg/m^2 or at a dose of about 1000 mg/m^2.

~~56. The method of claim 55, wherein the capecitabine is administered to the subject at a dose of about 1000 mg/m^2.~~

~~57. The method of claim 55 or 56, wherein the capecitabine is administered to the subject orally.~~

~~58.~~9. The use according to claim 8~~method of any one of claims 55-57~~, wherein the capecitabine is to be administered to the subject twice per day.

~~59.~~10. The use according to any one of claims 1-9~~method of any one of claims 1-58~~, wherein the trastuzumab is to be administered to the subject at a dose of about 400 mg to about 800 mg, or at a dose of about 4 mg/kg to about 10 mg/kg, or at a dose of about 6 mg/kg, or at a dose of about 8mg/kg.

~~60.~~11. The use according to claim 10~~method of claim 59~~, wherein the trastuzumab is to be administered to the subject at a dose of about 600 mg or at an initial dose of about 8 mg/kg followed by subsequent doses of about 6 mg/kg.

~~61. The method of claim 59 or 60, wherein the trastuzumab is administered to the subject subcutaneously.~~

~~62. The method of any one of claims 1-58, wherein the trastuzumab is administered to the subject at a dose of about 4 mg/kg to about 10 mg/kg.~~

~~63. The method of claim 62, wherein the trastuzumab is administered to the subject at a dose of about 6 mg/kg.~~

~~64. The method of claim 62, wherein the trastuzumab is administered to the subject at a dose of about 8 mg/kg.~~

~~65. The method of claim 62, wherein the trastuzumab is administered to the subject at an initial dose of about 8 mg/kg followed by subsequent doses of about 6 mg/kg.~~

~~66.~~12. The use according to any one of claims 1-11~~method of any one of claims 62-65~~, wherein the trastuzumab is to be administered intravenously or subcutaneously.

~~67.~~13. The use according to any one of claims 1-12~~method of any one of claims 59-66~~, wherein the trastuzumab is to be administered once about every 1 week, once about every 2 weeks, once about every 3 weeks, or once about every 4 weeks.

~~68. The method of claim 67, wherein the trastuzumab is administered once about every 3 weeks.~~

~~69.~~14. The use according to any one of claims 1-13~~method of any one of claims 1-68~~, wherein the tucatinib, capecitabine and trastuzumab are to be administered to the subject on a 21 day treatment cycle; or

wherein the tucatinib is to be administered to the subject twice per day on each day of the 21 day treatment cycle, and/or the capecitabine is to be administered to the subject twice

per day on each of days 1-14 of the 21 day treatment cycle, and/or the trastuzumab is to be administered to the subject once per 21 day treatment cycle; or

wherein the dose of trastuzumab during the first 21 day treatment cycle is 8 mg/kg and the dose of trastuzumab during the subsequent 21 day treatment cycles is 6 mg/kg.

~~70. The method of claim 69, wherein the tucatinib is administered to the subject twice per day on each day of the 21 day treatment cycle.~~

~~71. The method of claim 69 or 70, wherein the capecitabine is administered to the subject twice per day on each of days 1-14 of the 21 day treatment cycle.~~

~~72. The method of any one of claims 69-71, wherein the trastuzumab is administered to the subject once per 21 day treatment cycle.~~

~~73. The method of claim 72, wherein the dose of trastuzumab during the first 21 day treatment cycle is 8 mg/kg and the dose of trastuzumab during the subsequent 21 day treatment cycles is 6 mg/kg.~~

~~74.~~15. The use according to any one of claims 1-14~~method of any one of claims 1-73~~, wherein the subject was previously treated with trastuzumab, pertuzumab, ado-trastuzumab (T-DM1), or combinations thereof, ~~at least one anticancer therapy~~ for the breast cancer.

~~75. The method of claim 74, wherein the least one anticancer therapy is an anti-HER2 antibody or anti-HER2 antibody-drug conjugate.~~

~~76. The method of claim 75, wherein the at least one previous anticancer therapy is selected from the group consisting of trastuzumab, pertuzumab, ado-trastuzumab (T-DM1), and combinations thereof.~~

~~77. The method of any one of claims 74-76, wherein the subject is refractory to the previous anticancer therapy.~~

~~78. The method of claim 74-77, wherein the subject developed a brain metastasis during the previous anticancer therapy.~~

~~79. The method of any one of claims 1-78, wherein the subject has not been treated with another therapeutic agent for the breast cancer within the past 12 months.~~

~~80. The method of any one of claims 1-73, wherein the subject has not previously been treated with another therapeutic agent for the breast cancer.~~

~~81. The method of any one of claims 1-73, wherein the subject has not previously been treated with lapatinib, neratinib, afatinib, or capecitabine.~~