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 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 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 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 examples, regression of an existing brain metastasis in the subject has been promoted. In some 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 examples, the subject is exhibiting symptoms of diarrhea. In other 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. 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.
2. The use according to 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 use according to claim 1 or 2, 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.
5. The use according to any one of claims 1-4, 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.
6. The use according to claim 5, wherein the tucatinib is to be administered once or twice per day.
7. The use according to claim 6, wherein the tucatinib is to be administered to the subject at a dose of about 300 mg twice per day.

8. The use according to any one of claims 1-7, 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.

9. The use according to claim 8, wherein the capecitabine is to be administered to the subject twice per day.

10. The use according to any one of claims 1-9, 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.

11. The use according to claim 10, 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.

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

13. The use according to any one of claims 1-12, 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.

14. The use according to any one of claims 1-13, 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.

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