6,333,398; 6,797,814; 6,339,142; 6,417,335; 6,489,447; 7,074,404; 7,531,645; 7,846,441; 7,892,549; 8,075,892; 6,573,043; 6,905,830; 7,129,051; 7,344,840; 7,468,252; 7,674,589; 7,919,254; 6,949,245; 7,485,302; 7,498,030; 7,501,122; 7,537,931; 7,618,631; 7,862,817; 7,041,292; 6,627,196; 7,371,379; 6,632,979; 7,097,840; 7,575,748; 6,984,494; 7,279,287; 7,811,773; 7,993,834; 8,076,066; 8,044,017; 7,435,797; 7,850,966; 7,485,704; 7,807,799; 8,142,784; 7,560,111; 7,879,325; 8,241,630; 7,449,184; 8,163,287; 7,700,299; 7,981,418; 8,247,397; and US 2010/0016556; US 2005/0244929; US 2001/0014326; US 2003/0202972; US 2006/0099201; US 2010/0158899; US 2011/0236383; US 2011/0033460; US 2008/0286280; US 2005/0063972; US 2006/0182739; US 2009/0220492; US 2003/0147884; US 2004/0037823; US 2005/0002928; US 2007/0292419; US 2008/0187533; US 2011/0250194; US 2012/0034213; US 2003/0152987; US 2005/0100944; US 2006/0183150; US 2008/0050748; US 2009/0155803; US 2010/0120053; US 2005/0244417; US 2007/0026001; US 2008/0160026; US 2008/0241146; US 2005/0208043; US 2005/0238640; US 2006/0034842; US 2006/0073143; US 2006/0193854; US 2006/0198843; US 2011/0129464; US 2007/0184055; US 2007/0269429; US 2008/0050373; US 2006/0083739; US 2009/0087432; US 2006/0210561; US 2002/0035736; US 2002/0001587; US 2008/0226659; US 2002/0090662; US 2006/0046270; US 2008/0108096; US 2007/0166753; US 2008/0112958; US 2009/0239236; US 2012/0034609; US 2012/0093838; US 2004/0082047; US 2012/0065381; US 2009/0187007; US 2011/0159014; US 2004/0106161; US 2011/0117096; US 2004/0258685; US 2009/0148402; US 2009/0099344; US 2006/0034840; US 2011/0064737; US 2005/0276812; US 2008/0171040; US 2009/0202536; US 2006/0013819; US 2012/0107391; US 2006/0018899; US 2009/0285837; US 2011/0117097; US 2006/0088523; US 2010/0015157; US 2006/0121044; US 2008/0317753; US 2006/0165702; US 2009/0081223; US 2006/0188509; US 2009/0155259; US 2011/0165157; US 2006/0204505; US 2006/0212956; US 2006/0275305; US 2012/0003217; US 2007/0009976; US 2007/0020261; US 2007/0037228; US 2010/0112603; US 2006/0067930; US 2007/0224203; US 2011/0064736; US 2008/0038271; US 2008/0050385; US 2010/0285010; US 2011/0223159; US 2008/0102069; US 2010/0008975; US 2011/0245103; US 2011/0246399; US 2011/0027190; US 2010/0298156; US 2011/0151454; US 2011/0223619; US 2012/0107302; US 2009/0098135; US 2009/0148435; US 2009/0202546; US 2009/0226455; US 2009/0317387; US 2011/0044977; US 2012/0121586.

Summary

Disclosed is a method for extending progression free survival in a HER2-positive breast cancer patient population by 6 months or more comprising administering Pertuzumab, Trastuzumab and chemotherapy (e.g. taxane, such as Docetaxel) to the patients in the population. Optionally the method results in an objective response rate of 80% or more in the patients in the population. The the breast cancer is optionally metastatic or locally recurrent, unresectable breast cancer, or *de novo* Stage IV disease. In one embodiment, the patients in the population: have not received previous treatment or have relapsed after adjuvant therapy, have a left ventricular

ejection fraction (LVEF) of ≥50% at baseline, and/or have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Optionally, the HER2-positive breast cancer is defined as immunohistochemistry (IHC) 3+ and/or fluorescence *in situ* hybridization (FISH) amplification ratio ≥2.0. Optionally, the method reduces the risk of death by about 34% or more relative to a patient treated with Trastuzumab and the chemotherapy. In one aspect, there is provided use of Pertuzumab in the manufacture of a medicament for extending progression free survival in a HER2-positive breast cancer patient population by 6 months or more, wherein the medicament is to be administered with Trastuzumab and chemotherapy to the patients in the population, wherein the patients in the population have a left ventricular ejection fraction (LVEF) of ≥50% at baseline.

Disclosed is a method of combining two HER2 antibodies to treat HER2-positive cancer without increasing cardiac toxicity in a HER2-positive cancer patient population, comprising administering Pertuzumab, Trastuzumab, and chemotherapy to the patients in the population. Optionally, cardiac toxicity in the patient population is monitored for incidence of symptomatic left ventricular systolic dysfunction (LVSD) or congestive heart failure (CHF), or for decrease in left ventricular ejection fraction (LVEF). The HER2-positive cancer is optionally, breast cancer, for example metastatic or locally recurrent, unresectable breast cancer, or *de novo* Stage IV disease.In one aspect, there is provided use of two HER2 antibodies in the manufacture of a medicament to treat HER2-positive cancer without increasing cardiac toxicity in a HER2-positive cancer patient population, wherein Pertuzumab, Trastuzumab, and chemotherapy are to be administered to the patients in the population, wherein cardiac toxicity in the patient population is monitored for incidence of symptomatic left ventricular systolic dysfunction (LVSD) or congestive heart failure (CHF), or decrease in left ventricular ejection fraction (LVEF).

Disclosed is an article of manufacture comprising a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4 and/or the efficacy data in Table 2, Table 5, Figure 8, or Figure 10. In one aspect, there is provided an article of manufacture comprising a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4.

The disclosure additionally concerns a method for making an article of manufacture comprising packaging together a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4 and/or the efficacy data in Table 2, Table 5, Figure 8, or Figure 10. In one aspect, there is provided a method for making an article of manufacture comprising packaging together a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4.

Disclosed is a method of ensuring safe and effective use of Pertuzumab comprising packaging together a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4 and/or the efficacy data in Table 2, Table 5, Figure 8, or Figure 10. In one aspect, there is provided a method of ensuring safe and effective use of Pertuzumab comprising packaging together a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4 and the efficacy data in Table 2, Table 5, Figure 8, or Figure 10.

Optionally, the article of manufacture comprises a single-dose vial containing about 420mg of Pertuzumab.

Optionally, the package insert further comprises the warning box in Example 4.

Optionally, the package insert further provides the Overall Survival (OS) efficacy data in Example 9 or Table 14.

Disclosed is a method of treating early-stage HER2-positive breast cancer comprising administering Pertuzumab, Trastuzumab, and chemotherapy to a patient with the breast cancer, wherein the chemotherapy comprises anthracycline-based chemotherapy (for example, 5-FU, epirubicin, and cyclophosphamide (FEC)), or carboplatin-based chemotherapy (for example, Docetaxel and Carboplatin). Optionally, Pertuzumab is administered concurrently with the anthracycline-based chemotherapy or the carboplatin-based chemotherapy. In one embodiment of this method, Pertuzumab administration does not increase cardiac toxicity relative to the treatment

without Pertuzumab. Such treatment of early-stage HER2-positive breast cancer optionally comprises neoadjuvant or adjuvant therapy.

The disclosure further concerns a method of treating HER2-positive cancer in a patient comprising co-administering a mixture of Pertuzumab and Trastuzumab from the same intravenous bag to the patient. Such method optionally further comprises administering chemotherapy to the patient.

Also disclosed is an intravenous (IV) bag containing a stable mixture of Pertuzumab and Trastuzumab suitable for administration to a cancer patient. The mixture is optionally in saline solution; e.g. comprising about 0.9% NaCl or about 0.45% NaCl. The IV bag is optionally a 250mL 0.9% saline polyolefin or polyvinyl chloride infusion bag. In one embodiment, the IV bag which contains a mixture of about 420mg or of about 840mg of Pertuzumab and from about 200mg to about 1000mg of Trastuzumab. In one embodiment, the mixture is stable for up to 24 hours at 5°C or 30°C. Stability of the mixture can be evaluated by one or more assays selected from: color, appearance and clarity (CAC), concentration and turbidity analysis, particulate analysis, size exclusion chromatography (SEC), ion-exchange chromatography (IEC), capillary zone electrophoresis (CZE), image capillary isoelectric focusing (iCIEF), or potency assay.

The present disclosure provides a new treatment regimen for gastric cancer. In particular, the present disclosure concerns the treatment of HER2-positive gastric cancer in human subjects with a combination of Trastuzumab, Pertuzumab and at least one chemotherapy.

Disclosed is a method of treating HER2-positive gastric cancer in a human subject, comprising administering to the subject Pertuzumab, Trastuzumab, and a chemotherapy. In one aspect, there is provided use of Pertuzumab in the manufacture of a medicament for treating HER2-positive gastric cancer in a human subject, wherein the medicament is to be administered with Trastuzumab, and chemotherapy to the subject with HER2-positive gastric cancer.

Disclosed is a method of treating gastric cancer in a human subject comprising administering Pertuzumab to the subject with gastric cancer, wherein Pertuzumab is administered at a dose of 840 mg in all treatment cycles. In one aspect, there is provided use of Pertuzumab in the manufacture of a medicament for treating gastric cancer in a human subject , wherein the Pertuzumab is to be administered at a dose of 840 mg in all treatment cycles to the subject with gastric cancer.

Disclosed is a method of improving survival in a human subject with HER2-positive gastric cancer, comprising administering to the subject Pertuzumab, Trastuzumab, and a chemotherapy.

Disclosed is Pertuzumab for use in the treatment of HER2- positive gastric cancer in a human subject in combination with Trastuzumab and a chemotherapy.

Disclosed is the use of Pertuzumab in the preparation of a medicament for the treatment of HER2-positive gastric cancer, wherein the treatment comprises administration of Pertuzumab in combination with Trastuzumab and a chemotherapy.

Disclosed is the use of Trastuzumab in the preparation of a medicament for the treatment of HER2-positive gastric cancer, wherein the treatment comprises administration of Trastuzumab in combination with Pertuzumab and a chemotherapy.

Disclosed is a kit comprising a container comprising Pertuzumab and instructions for administration of the Pertuzumab to treat HER2-positive gastric cancer in a subject in combination with Trastuzumab and a chemotherapy.

Disclosed is a kit comprising a container comprising Trastuzumab and instructions for administration of the Trastuzumab to treat HER2-positivegastric cancer in a subject in combination with Pertuzumab and a chemotherapy.

In all aspects, the gastric cancer can, for example, be non-resectable locally advanced gastric cancer, or metastatic gastric cancer, or advanced, post-operatively recurrent gastric cancer, which may not be amenable to curative therapy by known methods. In all aspects, the gastric cancer includes adenocarcinoma of the stomach or gastroesophageal junction. In all aspects, in a particular embodiment the patient did not receive prior anti-cancer treatment for metastatic gastric cancer. In all aspects, in a particular embodiment, the chemotherapy comprises administration of a platin and/or fluoropyrimidine. In certain embodiments, the platin is cisplatin. In other embodiments, the fluoropyrimidine comprises capecitabine and/or 5-fluorouracil (5-FU). In all aspects, the patient's HER2-positive status may, for example, be IHC 3+ or IHC 2+/ISH+. In all aspects, in particular embodiments, the treatment improves survival, including overall survival (OS) and/or progression free survival (PFS) and/or response rate (RR). In all aspects, in particular embodiments, the patient has an ECOG PS of 0-1. In all aspects, treatment cycles are generally separated from each other by four weeks or less, or by three weeks or less, or by two weeks or less, or by one week or less.

Disclosed is a method of treating HER2-positive non-resectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction in a human patient who did not receive prior chemotherapy for metastatic disease, except prior adjuvant or neoadjuvant therapy completed more than six months before the current treatment, comprising administering Pertuzumab, Trastuzumab, cisplatin, and capecitabine and/or fluorouracil (5-FU) to the patient in an amount to improve progression free survival (PFS) and/or overall survival (OS), wherein the patient has an ECOG PS of 0-1. In a particular embodiment, the patient did not receive prior treatment with a platin.

Disclosed is a method of improving progression free survival in a patient with HER2-positive non-resectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction comprising administering Pertuzumab to the patient in combination with Trastuzumab and chemotherapy.

Disclosed is a method of treating HER2-positive breast cancer in a patient comprising administering Pertuzumab, Trastuzumab and vinorelbine to the patient. Optionally the Pertuzumab and Trastuzumab are co-administered to the patient from a single intravenous bag. The breast cancer is optionally metastatic or locally advanced. In one embodiment, the patient has not previously received systemic non-hormonal anticancer therapy in the metastatic setting.

Disclosed is a method of treating HER2-positive breast cancer in a patient comprising administering Pertuzumab, Trastuzumab, and aromatase inhibitor (e.g. anastrazole or letrozole) to the patient. Optionally, the breast cancer is hormone receptor-positive advanced breast cancer, wherein the hormone receptor is estrogen receptor (ER) and/or progesterone receptor (PgR), for example. According to this embodiment of the disclosure, patient has not previously received systemic nonhormonal anticancer therapy in the metastatic setting. Moreover, the patient herein optionally receives induction chemotherapy (e.g. comprising taxane). In one aspect, there is provided use of Pertuzumab in the manufacture of a medicament for treating HER2-positive breast cancer in a patient, wherein the medicament is to be administered with Trastuzumab, and aromatase inhibitor.

In an additional embodiment, the disclosure concerns a method of treating a cancer patient comprising administering to the patient an initial dose of 840mg of Pertuzumab followed every 3 weeks thereafter by a dose of 420mg of Pertuzumab, and further comprising re-administering an 840mg dose of Pertuzumab to the patient if the time between two sequential 420mg doses is 6 weeks or more. Optionally, the method further comprises administering 420mg of Pertuzumab every 3 weeks after the re-administered 840mg dose. In one embodiment, the cancer patient has HER2-positive breast cancer. In one aspect, there is provided use of Pertuzumab in the manufacture of a medicament for treating a cancer patient wherein the patient is to be administered an initial dose of 840mg of Pertuzumab followed every 3 weeks thereafter by a dose of 420mg of Pertuzumab, and further re-administered an 840mg dose of Pertuzumab if the time between two sequential 420mg doses is 6 weeks or more.

Disclosed is a method for treating HER2-positive metastatic or locally recurrent breast cancer in a patient comprising administering Pertuzumab, Trastuzumab and taxoid (e.g. Docetaxel, Paclitaxel, or *nab*-paclitaxel) to the patient, wherein the patient has been previously treated with a Trastuzumab and/or lapatinib as adjuvant or neoadjuvant therapy. In one aspect, there is provided use of Pertuzumab in the manufacture of a medicament for treating HER2-positive metastatic or locally recurrent breast cancer in a patient, wherein the medicament is to be administered withTrastuzumab and taxoid, wherein the patient has been previously treated with a Trastuzumab and/or lapatinib as adjuvant or neoadjuvant therapy, wherein the taxoid is Paclitaxel or *nab*-paclitaxel.

Disclosed is a method for treating low HER3 ovarian, primary peritoneal, or fallopian tube cancer in a patient comprising administering Pertuzumab and chemotherapy the patient, wherein the chemotherapy comprises taxoid (e.g. paclitaxel) or topotecan.

Disclosed is a method for treating low HER3 ovarian, primary peritoneal, or fallopian tube cancer in a patient comprising administering Pertuzumab and chemotherapy to the patient, wherein the low HER3 cancer expresses HER3 mRNA at a concentration ratio equal or lower than about 2.81 as assessed by polymerase chain reaction (PCR). In one embodiment, the chemotherapy comprises gemcitabine, carboplatin, paclitaxel, docetaxel, topotecan, or pegylated liposomal doxorubicin (PLD). Optionally, the chemotherapy comprises paclitaxel or topotecan. In one embodiment, the cancer is epithelial ovarian cancer that is platinum-resistant or platinum-refractory.

Brief Description of the Drawings

Figure 1 provides a schematic of the HER2 protein structure, and amino acid sequences for Domains I-IV (SEQ ID Nos.1-4, respectively) of the extracellular domain thereof.

Figures 2A and 2B depict alignments of the amino acid sequences of the variable light (V_L) (Fig. 2A) and variable heavy (V_H) (Fig. 2B) domains of murine monoclonal antibody 2C4 (SEQ ID Nos. 5 and 6, respectively); V_L and V_H domains of variant 574/Pertuzumab (SEQ ID Nos. 7 and 8, respectively), and human V_L and V_H consensus frameworks (hum κ1, light kappa subgroup I; humIII, heavy subgroup III) (SEQ ID Nos. 9 and 10, respectively). Asterisks identify differences between

WHAT IS CLAIMED IS:

1. Use of Pertuzumab in the manufacture of a medicament for treating gastric cancer in a human subject , wherein the Pertuzumab is to be administered at a dose of 840 mg in all treatment cycles to the subject with gastric cancer.

2. The use of claim 1 wherein Pertuzumab is to be administered at the dose of 840 mg for six treatment cycles.

3. The use of claim 1 or claim 2 which maintains Pertuzumab through levels above about 20 μg/mL in the subject.

4. The use of any one of claims 1 to 4 wherein Trastuzumab and chemotherapy are to be administered to the subject.

5. Use of Pertuzumab in the manufacture of a medicament for treating HER2-positive gastric cancer in a human subject, wherein the medicament is to be administered with Trastuzumab, and chemotherapy to the subject with HER2-positive gastric cancer.

6. The use of claim 5 wherein the gastric cancer comprises non-resectable locally advanced gastric cancer, or metastatic gastric cancer, or advanced, post-operatively recurrent gastric cancer, which may not be amenable to curative therapy by known methods, or adenocarcinoma of the stomach or gastroesophageal junction.

7. The use of claim 5 or claim 6 wherein the patient has not received prior anti-cancer treatment for metastatic gastric cancer, has an Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) of 0-1, or has a HER2-positive status of IHC 3+ or IHC2+/ISH+.

8. The use of any one of claims 5 to 7 wherein the chemotherapy comprises platin (cisplatin) and/or fluoropyrimidine (capecitabine or 5-fluorouracil (5-FU)).

9. The use of claim 8 wherein Pertuzumab, Trastuzumab, cisplatin, and capecitabine or 5-FU are to be administered.

10. The use of any one of claims 5 to 9 wherein Pertuzumab is to be administered at a dose of 840 mg in all treatment cycles.

11. The use of any one of claims 5 to 10 which improves overall survival (OS) relative to a patient treated with Trastuzumab and the chemotherapy only, or improves progression free survival (PFS) or response rate (RR) relative to treatment with Trastuzumab and chemotherapy only.

12. Use of Pertuzumab in the manufacture of a medicament for extending progression free survival in a HER2-positive breast cancer patient population by 6 months or more, wherein the medicament is to be administered with Trastuzumab and chemotherapy to the patients in the population, wherein the patients in the population have a left ventricular ejection fraction (LVEF) of ≥50% at baseline.

13. The use of claim 12 which results in an objective response rate of 80% or more in the patients in the population.

14. The use of claim 12 or claim 13 wherein the chemotherapy comprises taxane.

15. The use of claim 14 wherein the taxane is Docetaxel.

16. The use of any one of claims 12 to 15 wherein the breast cancer is metastatic or locally recurrent, unresectable breast cancer, or *de novo* Stage IV disease.

17. The use of any one of claims 12 to 16 wherein the patients in the population have not received previous treatment or have relapsed after adjuvant therapy.

18. The use of any one of claims 12 to 17 wherein the HER2-positive breast cancer is defined as immunohistochemistry (IHC) 3+ and/or fluorescence *in situ* hybridization (FISH) amplification ratio ≥2.0.

19. The use of any one of claims 12 to 18 wherein the patients in the population have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

20. Use of two HER2 antibodies in the manufacture of a medicament to treat HER2-positive cancer without increasing cardiac toxicity in a HER2-positive cancer patient population, wherein Pertuzumab, Trastuzumab, and chemotherapy are to be administered to the patients in the population, wherein cardiac toxicity in the patient population is monitored for incidence of symptomatic left ventricular systolic dysfunction (LVSD) or congestive heart failure (CHF), or decrease in left ventricular ejection fraction (LVEF).

21. The use of claim 20 wherein the HER2-positive cancer is breast cancer.

22. The use of claim 20 or claim 21 wherein the breast cancer is metastatic or locally recurrent, unresectable breast cancer, or *de novo* Stage IV disease.

23. An article of manufacture comprising a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4.

24. The article of manufacture of claim 23 wherein the package insert provides the efficacy data in Table 2, Table 5, Figure 8, or Figure 10.

25. The article of manufacture of claim 23 or claim 24 wherein the vial is a single-dose vial containing about 420mg of Pertuzumab.

26. A method for making an article of manufacture comprising packaging together a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4.

27. A method of ensuring safe and effective use of Pertuzumab comprising packaging together a vial with Pertuzumab therein and a package insert, wherein the package insert provides the safety data in Table 3 or Table 4 and the efficacy data in Table 2, Table 5, Figure 8, or Figure 10.

28. Use of Pertuzumab in the manufacture of a medicament for treating a cancer patient wherein the patient is to be administered an initial dose of 840mg of Pertuzumab followed every 3 weeks thereafter by a dose of 420mg of Pertuzumab, and further re-administered an 840mg dose of Pertuzumab if the time between two sequential 420mg doses is 6 weeks or more.

29. The use of claim 28 wherein 420mg of Pertuzumab is to be administered every 3 weeks after the re-administered 840mg dose.

30. The use of claim 28 or claim 29 wherein the cancer patient has HER2-positive breast cancer.

31. Use of Pertuzumab in the manufacture of a medicament for treating HER2-positive metastatic or locally recurrent breast cancer in a patient, wherein the medicament is to be administered withTrastuzumab and taxoid, wherein the patient has been previously treated with a Trastuzumab and/or lapatinib as adjuvant or neoadjuvant therapy, wherein the taxoid is Paclitaxel or *nab*-paclitaxel.

32. The use of claim 31 wherein the patient has been previously treated with Trastuzumab as neoadjuvant therapy.

33. Use of Pertuzumab in the manufacture of a medicament for treating HER2-positive breast cancer in a patient, wherein the medicament is to be administered with Trastuzumab, and aromatase inhibitor.

34. The use of claim 33 wherein the aromatase inhibitor is anastrazole or letrozole.

35. The use of claim 33 or claim 34 wherein the breast cancer is hormone receptor-positive advanced breast cancer.

36. The use of claim 35 wherein the hormone receptor is estrogen receptor (ER) and/or progesterone receptor (PgR).

37. The use of any one of claims 33 to 36 wherein the patient has not previously received systemic nonhormonal anticancer therapy in the metastatic setting.

38. The use of any one of claims 33 to 36 wherein the patient receives induction chemotherapy.

39. The use of claim 38 wherein the induction chemotherapy comprises a taxane.