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 ~~of the Invention~~

~~In a first aspect, the invention concerns~~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 another aspect, the invention concerns~~Also 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 another aspect, the invention concerns~~Further 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.

The ~~invention~~ 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 a related ~~aspect~~embodiment, the ~~invention~~ disclosure concerns 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.

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.

In one aspect, there is provided use of Pertuzumab, Trastuzumab, and carboplatin-based chemotherapy in the manufacture of a medicament for treating early-stage HER2-positive breast cancer in a patient, wherein the carboplatin-based chemotherapy comprises Docetaxel and Carboplatin.

~~In another aspect, the invention concerns~~Also 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 ~~invention~~ 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.

In a related ~~aspect~~embodiment, the ~~invention~~ disclosure provides 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~~invention~~ provides a new treatment regimen for gastric cancer. In particular, the present disclosure~~invention~~ concerns the treatment of HER2-positivegastric cancer in human subjects with a combination of Trastuzumab, Pertuzumab and at least one chemotherapy.

In one ~~aspect~~embodiment, the disclosure~~invention~~ concerns 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~~embodiment, the disclosure~~invention~~ concerns 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 another ~~aspect~~embodiment, the disclosure~~invention~~ concerns a method of improving survival in a human subject with HER2-positive gastric cancer, comprising administering to the subject Pertuzumab, Trastuzumab, and a chemotherapy.

In yet another embodiment~~aspect~~, the disclosure~~invention~~ concerns Pertuzumab for use in the treatment of HER2- positive gastric cancer in a human subject in combination with Trastuzumab and a chemotherapy.

In a further embodiment~~aspect~~, the disclosure~~invention~~ concerns 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.

In a still further embodiment~~aspect~~, the disclosure~~invention~~ concerns 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.

In another embodimentaspect, the disclosureinvention concerns 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.

In yet another embodimentaspect, the disclosureinvention concerns 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 embodimentsaspects, 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 embodimentsaspects, 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 aspectsembodiments, the patient's HER2-positive status may, for example, be IHC 3+ or IHC 2+/ISH+. In all aspectsembodiments, 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 embodimentsaspects, 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.

In a particular embodimentaspect, the disclosureinvention concerns 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.

In another embodimentaspect, the disclosureinvention concerns 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.

In yet a further embodimentaspect, the disclosureinvention concerns 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.

In another embodimentaspect, the disclosureinvention concerns 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 disclosureinvention, 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 an additional embodiment, the disclosureinvention 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 a further embodimentaspect, the disclosureinvention concerns 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 yet a further embodimentaspect, the disclosureinvention concerns 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.

In an additional embodimentaspect, the disclosureinvention concerns 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, Trastuzumab, and carboplatin-based chemotherapy in the manufacture of a medicament for treating early-stage HER2-positive breast cancer in a patient, wherein the carboplatin-based chemotherapy comprises Docetaxel and Carboplatin.

2. The use according to claim 1, wherein the Pertuzumab is to be administered concurrently with the carboplatin-based chemotherapy.

3. The use according to claim 1 or 2, wherein the medicament is to be used in a neoadjuvant or adjuvant therapy.

WHAT IS CLAIMED IS:

1. 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 to the patients in the population.

2. The method of claim 1 which results in an objective response rate of 80% or more in the patients in the population.

3. The method of claim 1 or claim 2 wherein the chemotherapy comprises taxane.

4. The method of claim 3 wherein the taxane is Docetaxel.

5. The method of any one of claims 1 to 4 wherein the breast cancer is metastatic or locally recurrent, unresectable breast cancer, or *de novo* Stage IV disease.

6. The method of any one of claims 1 to 5 wherein the patients in the population have not received previous treatment or have relapsed after adjuvant therapy.

7. The method of any one of claims 1 to 6 wherein the HER2-positive breast cancer is defined as immunohistochemistry (IHC) 3+ and/or fluorescence *in situ* hybridization (FISH) amplification ratio ≥2.0.

8. The method of any one of claims 1 to 7 wherein the patients in the population have a left ventricular ejection fraction (LVEF) of ≥50% at baseline.

9. The method of any one of claims 1 to 8 wherein the patients in the population have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

10. 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.

11. The method of claim 10 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).

12. The method of claim 10 or claim 11 wherein the HER2-positive cancer is breast cancer.

13. The method of any one of claims 10 to 12 wherein the breast cancer is metastatic or locally recurrent, unresectable breast cancer, or *de novo* Stage IV disease.

14. 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.

15. The article of manufacture of claim 14 wherein the package insert provides the efficacy data in Table 2, Table 5, Figure 8, or Figure 10.

16. The article of manufacture of claim 14 or claim 15 wherein the vial is a single-dose vial containing about 420mg of Pertuzumab.

17. 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.

18. 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.

19. 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, or carboplatin-based chemotherapy.

20. The method of claim 19 wherein chemotherapy comprises anthracycline-based chemotherapy which comprises 5-FU, epirubicin, and cyclophosphamide (FEC).

21. The method of claim 20 wherein the Pertuzmab is administered concurrently with the anthracycline-based chemotherapy.

22. The method of claim 19 wherein the chemotherapy comprises carboplatin-based chemotherapy which comprises Docetaxel and Carboplatin.

23. The method of claim 22 wherein the Pertuzmab is administered concurrently with the carboplatin-based chemotherapy.

24. The method of any one of claims 19 to 23 wherein Pertuzumab administration does not increase cardiac toxicity relative to the treatment without Pertuzumab.

25. The method of any one of claims 19 to 24 which comprises neoadjuvant or adjuvant therapy.

26. 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.

27. The method of claim 26 which further comprises administering chemotherapy to the patient.

28. An intravenous (IV) bag containing a stable mixture of Pertuzumab and Trastuzumab suitable for administration to a cancer patient.

29. The IV bag of claim 28 wherein the mixture is in saline solution.

30. The IV bag of claim 29 wherein the saline solution comprises about 0.9% NaCl or about 0.45% NaCl.

31. The IV bag of any one of claims 28 to 30 which is a 250mL 0.9% saline polyolefin or polyvinyl chloride infusion bag.

32. The IV bag of any one of claims 28 to 31 which contains a mixture of about 420mg or about 840mg of Pertuzumab and from about 200mg to about 1000mg of Trastuzumab.

33. The IV bag of any one of claims 28 to 32 wherein the mixture is stable for up to 24 hours at 5°C or 30°C.

34. The IV bag of any one of claims 28 to 33 wherein stability has been evaluated by an assay selected from the group consisting of: 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), and potency assay.

35. A method of treating HER2-positive gastric cancer in a human subject comprising administering Pertuzumab, Trastuzumab, and chemotherapy to the subject with HER2-positive gastric cancer.

36. The method of claim 35 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.

37. The method of claim 35 or claim 36 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+.

38. The method of any one of claims 35 to 37 wherein the chemotherapy comprises platin (cisplatin) and/or fluoropyrimidine (capecitabine or 5-fluorouracil (5-FU)).

39. The method of claim 38 wherein Pertuzumab, Trastuzumab, cisplatin, and capecitabine or 5-FU are administered.

40. The method of any one of claims 35 to 39 wherein Pertuzumab is administered at a dose of 840 mg in all treatment cycles.

41. The method of any one of claims 35 to 40 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.

42. 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.

43. The method of claim 42 wherein Pertuzumab is administered at the dose of 840 mg for six treatment cycles.

44. The method of claim 42 or claim 43 which maintains Pertuzumab trough levels above about 20 μg/mL in the subject.

45. The method of any one of claims 42 to 44 further comprising administering Trastuzumab and chemotherapy to the subject.

46. 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 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 Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) of 0-1.

47. A method of improving progression free survival (PFS) in a human 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.

48. A method of treating HER2-positive breast cancer in a patient comprising administering Pertuzumab, Trastuzumab and vinorelbine to the patient.

49. The method of claim 48 wherein the Pertuzumab and Trastuzumab are co-administered to the patient from a single intravenous bag.

50. The method of claim 48 or claim 49 wherein the breast cancer is metastatic or locally advanced.

51. The method of any one of claims 48 to 50 wherein the patient has not previously received systemic non-hormonal anticancer therapy in the metastatic setting.

52. A method of treating HER2-positive breast cancer in a patient comprising administering Pertuzumab, Trastuzumab, and aromatase inhibitor to the patient.

53. The method of claim 52 wherein the aromatase inhibitor is anastrazole or letrozole.

54. The method of claim 52 or claim 53 wherein the breast cancer is hormone receptor-positive advanced breast cancer.

55. The method of claim 54 wherein the hormone receptor is estrogen receptor (ER) and/or progesterone receptor (PgR).

56. The method of any one of claims 52 to 55 wherein the patient has not previously received systemic nonhormonal anticancer therapy in the metastatic setting.

57. The method of any one of claims 52 to 56 wherein the patient receives induction chemotherapy.

58. The method of claim 57 wherein the induction chemotherapy comprises a taxane.

59. The method of claim 17 or claim 18 wherein the package insert further comprises the warning box in Example 4.

60. 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.

61. The method of claim 60 further comprising administering 420mg of Pertuzumab every 3 weeks after the re-administered 840mg dose.

62. The method of claim 60 or claim 61 wherein the cancer patient has HER2-positive breast cancer.

63. The method of any one of claims 1 to 13 which which reduces the risk of death by about 34% or more relative to a patient treated with Trastuzumab and the chemotherapy.

64. The method of claim 17 or claim 18 wherein the package insert further provides the Overall Survival (OS) efficacy data in Example 9 or Table 14.

65. A method for treating HER2-positive metastatic or locally recurrent breast cancer in a patient comprising administering Pertuzumab, Trastuzumab and taxoid to the patient, wherein the patient has been previously treated with a Trastuzumab and/or lapatinib as adjuvant or neoadjuvant therapy.

66. The method of claim 65 wherein the taxoid is Docetaxel, Paclitaxel, or *nab*-paclitaxel.

67. The method of claim 65 wherein the taxoid is Paclitaxel or *nab*-paclitaxel.

68. The method of any one of claims 65 to 67 wherein the patient has been previously treated with Trastuzumab as neoadjuvant therapy.

69. 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).

70. The method of claim 69 wherein the chemotherapy comprises gemcitabine, carboplatin, paclitaxel, docetaxel, topotecan, or pegylated liposomal doxorubicin (PLD).

71. The method of claim 70 wherein the chemotherapy comprises paclitaxel or topotecan.

72. The method of any one of claims 69 to 71 wherein the cancer is epithelial ovarian cancer that is platinum-resistant or platinum-refractory.