

Brand Name: Perjeta

Generic Name: pertuzumab

Manufacturer³: Genentech, Inc

Drug Class^{1,2,3}: Antineoplastic Agent, Anti-HER2, Monoclonal Antibody^{1,2}

Uses:

Labeled Uses^{1,2,3,4,5}: Treatment of HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel in patients who have not received prior anti-HER2 therapy or chemotherapy to treat metastatic disease.

Non-labeled Uses: Pertuzumab currently has no non-FDA approved indications.

Mechanism of Action:^{1,2,3,4,5}

Pertuzumab is a recombinant humanized monoclonal antibody that inhibits ligand-dependent heterodimerization of extracellular human epidermal growth factor receptor 2 protein (HER2) by targeting the extracellular dimerization domain. Two intracellular signaling pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K) are inhibited halting cell growth and initiating apoptosis. Pertuzumab binds to the dimerization domain of HER2 while trastuzumab binds to the juxtamembrane region. When pertuzumab is combined with trastuzumab, a more complete inhibition of HER2 signaling occurs, enhancing antitumor activity.

Pharmacokinetics^{1,2,3,4,5}:

Absorption:

T _{max}	Not reported
V _d	5.2L
t _{1/2}	18 days
Clearance	0.24L/day
Protein binding	Not reported
Bioavailability	Not reported

Metabolism: No documented reports

Elimination: No documented reports

Clinical Evidence:

Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, Clark E, Benyunes MC, Ross G, Swain SM; CLEOPATRA Study Group. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. N Engl J Med. 2012 Jan 12;366(2):109-19

Study design: Randomized, double-blind, placebo-controlled, phase 3 trial in patients with HER2-positive metastatic breast cancer who had not received chemotherapy or biologic therapy for their metastatic disease.

Description of study: All 808 subjects were randomized to receive placebo plus trastuzumab plus docetaxel or pertuzumab plus trastuzumab plus docetaxel as first line treatment until the time of disease progression or the development of toxic effects that could not be managed. Eligible patients had locally recurrent, unresectable, or metastatic HER-2 positive breast cancer. Patients may have received adjuvant or neoadjuvant chemotherapy with or without trastuzumab before randomization. Patients were given a fixed loading dose of 840 mg of pertuzumab or placebo, followed by 420 mg every 3 weeks. The primary endpoint was independently assessed progression-free survival. Secondary endpoints included overall survival, progression-free survival assessed by the investigator, the objective response rate and safety.

The median progression-free survival was statistically significantly longer with the pertuzumab group when compared to the placebo group ($p < 0.001$). The interim analysis of overall survival showed no significant difference between groups because it did not cross the O'Brien-Fleming stopping boundary threshold ($p = 0.005$). However, the data showed a strong trend towards a survival benefit with pertuzumab-trastuzumab-docetaxel therapy. Drug related adverse effects were generally similar in the two groups with no increase in left ventricular systolic dysfunction. The incidence of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin were higher in the pertuzumab group.

Limitations: La Roche/Genentech supported, sponsored, and designed the study. This study cannot be applied to newly diagnosed HER2 positive breast cancer.

Conclusions: Pertuzumab plus trastuzumab plus docetaxel when used as first line treatment for HER2-positive metastatic breast cancer significantly prolonged progression-free survival compared to placebo plus trastuzumab plus docetaxel. The interim analysis of overall survival showed no significant difference between groups even though the data showed a strong trend towards a survival benefit.

Gianni, L, Pienkowski T, Im, Y, Roman L, Tseng L, Liu M, Lluch, A, Staroslawska E, Haba-Rodriguez J, Im S, Luiz J, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagusaa P. Efficacy and Safety of Neoadjuvant Pertuzumab and Trastuzumab in Women with Locally Advanced, Inflammatory, or Early HER2-Positive Breast Cancer (NeoSphere): A Randomised Multicentre, Open-label, Phase-2 Trial. Lancet Oncol 2012 Jan;13:25-32.

Study design: NeoSphere was multicenter, international, randomized, open label, phase 2 trial in women with locally advanced, inflammatory, or early HER2-positive breast cancer.

Description of study: All 417 eligible subjects were randomized centrally and stratified by operable, locally advanced, and inflammatory breast cancer and by hormone receptor expression to receive four neoadjuvant cycles of: 8 mg/kg loading dose of trastuzumab plus docetaxel 6 mg/kg every 3 weeks plus a loading dose of 840 mg, followed by 420 mg every 3 weeks of pertuzumab or trastuzumab plus docetaxel or pertuzumab and trastuzumab or pertuzumab plus docetaxel. Eligible patients had centrally confirmed HER2-positive, operable, locally advanced, or inflammatory breast cancer with primary tumors larger than 2 cm in diameter. The primary endpoint was pathological complete response in the breast. Secondary endpoints included clinical response rate, time to clinical response, breast conserving surgery rate, and safety.

Patients given pertuzumab plus trastuzumab plus docetaxel had a significantly improved pathological complete response rate (49 of 107 patients; 45.8% [95% CI 36.1-55.7]) compared to those given trastuzumab plus docetaxel ($p=0.0141$). In the group given pertuzumab plus docetaxel, 23 of 96 (24.0% [95% CI 15.8 -33.7]) had pathological complete response, as did 18 of 107 (16.8% [95% CI 10.3-25.3]) given pertuzumab and trastuzumab. Drug related adverse effects such as neutropenia, febrile neutropenia, and leucopenia were similar among groups except patients receiving pertuzumab and trastuzumab experienced fewer adverse events. The mean LVEF decrease was balanced across treatment groups.

Limitations: La Roche supported and sponsored the study; some employees and affiliates of Roche and Genentech, and GlaxoSmithKline were investigators and helped design the study. This was an open-label study.

Conclusions: Pertuzumab plus trastuzumab plus docetaxel significantly improves pathological complete response rate compared with those given trastuzumab plus docetaxel. Pertuzumab and trastuzumab without chemotherapy eradicated tumors in a proportion of women and showed a favorable safety profile. Although pertuzumab plus docetaxel was efficacious, the combination of chemotherapy with both antibodies was more active than chemotherapy with either antibody alone.

Gianni L, Llado A, Bianchi G, Cortes J, Kellokumpu-Lehtinen P, Cameron D, Miles D, Salvagni S, Wardley A, Goeminne J, Hersberger V, Baselga J. Open-Label, Phase II, Multicenter, Randomized Study of the Efficacy and Safety of Two Dose Levels of Pertuzumab, a Human Epidermal Growth Factor Receptor 2 Dimerization Inhibitor, in Patients with Human Epidermal Growth Factor Receptor2-Negative Metastatic Breast Cancer. J Clin Oncol. 2010 Feb;28:1131-1137.

Study design: This was a multicenter, international, randomized, open label, phase 2 trial in patients with centrally confirmed HER2-negative metastatic breast cancer.

Description of study: All 79 patients were randomized to receive pertuzumab once every 3 weeks with a loading dose of 840 mg followed by either 420 mg or 1,050 mg. Eligible patients had a prior histologically documented diagnosis of breast cancer with a measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST), had metastatic disease treated with up

to two lines of chemotherapy, and had anthracycline-containing therapy either in adjuvant setting or for metastatic disease. Centrally confirmed lack of HER2 amplification or high expression was required. The primary endpoint was response rate for each treatment regimen per RECIST. Secondary endpoints included time to progression, time to treatment failure, time to response, duration of response, and rate of stable disease, and safety.

Of the 79 patients randomized, 78 were included in the intent to treat analysis. There were 2 patients in the 420 mg group who had partial responses lasting 18 weeks in one patient and 31 weeks in the other. In this same group, 18 experienced a stable disease lasting greater than 12 weeks. Of the patients who received 1,050 mg, stable disease was observed in 14 patients. Overall 6 out of 78 patients responded or had a stable disease greater than 6 months. Both dose levels were well tolerated. The most frequent toxicities were grade 1 to 2 diarrhea, asthenia, nausea, and vomiting. Decline in LVEF of greater than 10% and/or less than 50% was observed in eight patients, with one case of congestive heart failure in the 420 mg dose group.

Limitations: La Roche/Genentech supported and sponsored the study; some employees and affiliates of La Roche, Genentech, and GlaxoSmithKline were investigators and designed the study. The study was open label.

Conclusions: There was limited efficacy observed, due to a short duration of stable disease in approximately 40% of patients with HER2-negative breast cancer and only 7.7% of patients experiencing a clinical benefit with either a partial response or stable disease greater than 6 months. Therefore, the use of single-agent pertuzumab in HER-2 negative breast cancer was justified by preclinical evidence but did not meet expectations of clinical benefit in the metastatic setting.

Contraindications^{1,2,3,4,5}:

There are no well documented contraindications

Precautions^{1,2,3,4,5}:

Left ventricular dysfunction: Drugs that block HER2 activity, including pertuzumab have been reported to cause decreases in left ventricular ejection fraction (LVEF). Patients who have received anthracycline or radiotherapy in the past to the chest area may be at an increased risk of decreased LVEF. Patients LVEF should be assessed prior to starting pertuzumab and at regular intervals during treatment.

Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis: Pertuzumab has been associated with infusion and hypersensitivity reactions. Patients should be monitored for 60 minutes after the first infusion and 30 minutes after the subsequent infusion for infusion-related reactions such as anaphylactoid reaction and cytokine release syndrome. Slow or interrupt the infusion if a significant infusion-associated reaction occurs. Appropriate medical therapies should then be administered. Consider permanent discontinuation in patients with serious infusion reactions.

HER2 testing: The detection of HER2 protein overexpression is necessary for the selection of patients appropriate for pertuzumab therapy. Patients with HER2 overexpression are the only patients studied and for whom benefit has been shown.

Immunogenicity: There is the potential for an immune response to pertuzumab.

Pregnancy: Pertuzumab is a pregnancy category D and caused fetal harm when given to animals. If pertuzumab is administered during pregnancy or becomes pregnant while receiving this drug, the patient should be notified of potential hazard to a fetus. Women who become pregnant or intend to become pregnant should notify their physician.

Lactation: It is not known if pertuzumab is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, the decision to discontinue breast-feeding or pertuzumab should be made taking into account the importance of the drug to the mother. The extended half-life should be considered for decisions regarding breast feeding after treatment is completed.

Pediatrics Use: Safe and effective use for children has not been established.

Geriatric Use: No overall differences in the efficacy and safety of pertuzumab were observed between elderly and younger patients.

Adverse Effects^{1,2,3,4,5}:

The most common adverse reactions with pertuzumab in combination with trastuzumab and docetaxel, occurring in more than 30% of patients, were alopecia, diarrhea, fatigue, nausea, neutropenia, peripheral neuropathy, and rash.

Occurring in >10% of patients with pertuzumab in combination with trastuzumab and docetaxel

CNS:

- Asthenia (26% All grades; 2.5% Grades 3 to 4)
- Dizziness (12.5% All grades; 0.5% Grades 3 to 4)
- Fatigue (37.6 % All grades; 2.2% Grades 3 to 4)
- Headache (20.9 % All grades; 1.2% Grades 3 to 4)
- Insomnia (13.3 % All grades; 0% Grades 3 to 4)
- Neuropathy peripheral (32.4% All grades; 3.2% Grades 3 to 4)

Dermatologic

- Alopecia (60.9 % All grades; 0% Grades 3 to 4)
- Dry skin (10.6 % All grades; 0% Grades 3 to 4)
- Nail disorder (22.9 % All grades; 1.2% Grades 3 to 4)
- Pruritus (14 % All grades; 0% Grades 3 to 4)
- Rash (33.7 % All grades; 0.7% Grades 3 to 4)

Gastrointestinal

- Constipation (15 % All grades; 0% Grades 3 to 4)
- Decreased appetite (29.2 % All grades; 1.7% Grades 3 to 4)
- Diarrhea (66.8 % All grades; 7.9% Grades 3 to 4)
- Dysgeusia (18.4 % All grades; 0% Grades 3 to 4)

Nausea (42.3 % All grades; 1.2% Grades 3 to 4)
Stomatitis (18.9 % All grades; 0.5% Grades 3 to 4)
Vomiting (24.1 % All grades; 1.5% Grades 3 to 4)

Hematologic/Lymphatic

Anemia (23.1 % All grades; 2.5% Grades 3 to 4)
Febrile neutropenia (13.8 % All grades; 13% Grades 3 to 4)
Leukopenia (18.2 % All grades; 12.3% Grades 3 to 4)
Neutropenia (52.8 % All grades; 48.9% Grades 3 to 4)

Musculoskeletal

Arthralgia (15.5 % All grades; 0.2% Grades 3 to 4)
Myalgia (22.9 % All grades; .1.0% Grades 3 to 4)

Respiratory

Dyspnea (14.0 % All grades; 1.0% Grades 3 to 4)
Nasopharyngitis (11.8 % All grades; 0% Grades 3 to 4)
Upper respiratory tract infection (16.7 % All grades; 0.7% Grades 3 to 4)

Miscellaneous

Edema peripheral (23.1 % All grades; 0.5% Grades 3 to 4)
Lacrimation increased (14 % All grades; 0% Grades 3 to 4)
Mucosal inflammation (27.8 % All grades; 1.5% Grades 3 to 4)
Pyrexia (18.7% All grades; 1.2% Grades 3 to 4)

Occurring in <10% of patients

Cardiovascular

Left ventricular dysfunction (4.4%)
Symptomatic LVSD (CHF) (1%)

Miscellaneous

Hypersensitivity (10.1%)
Paronychia (7.1%)
Pleural effusion (5.2%)

Adverse reactions after discontinuing docetaxel were reported less frequently. All adverse reactions with pertuzumab and trastuzumab treatment occurred in less than 10% of patients with exceptions of diarrhea, upper respiratory tract infection, rash, headache, and fatigue.

Drug Interactions^{1,2,3,4,5}:

Minimally or noninteracting drugs: Drug interactions have not been reported with pertuzumab.

Abciximab can enhance the potential for allergic or hypersensitivity reactions to Monoclonal antibodies and may cause thrombocytopenia or diminished therapeutic effects².

Belimumab's adverse and toxic effects may be enhanced when administered with Monoclonal Antibodies.²

Dosage form and strengths³: 420 mg/14 mL single-use vial

Dosing/Administration^{1,2,3,4,5}:

Administration:

Pertuzumab should be administered for I.V. infusion only. Do not administer I.V. push or as a rapid bolus. Dilute in 250 mL 0.9% sodium chloride only in PVC or non PVC bags. Do not shake; gently invert the diluted solution to mix. Do not mix with other medications.

Adult Dosing

I.V.:Initial dose: 840 mg over 60 minutes followed by a maintenance dose of 420 mg over 30 to 60 minutes every 3 weeks until disease progression or unacceptable toxicity in combination with trastuzumab and docetaxel.

Elderly

Refer to adult dosing

Renal impairment

No dosage adjustment provided due to the fact it has not been studied.

Hepatic impairment

No dosage adjustment provided due to the fact it has not been studied.

Adjustment for Toxicity

Dose reductions are not recommended for pertuzumab. Pertuzumab and trastuzumab may be continued if docetaxel is discontinued. If trastuzumab is discontinued then pertuzumab should be discontinued.

Dosing Modification^{1,2,3,4,5}

Delayed or Missed dose

If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of pertuzumab should be administered. Do not wait until the next planned dose.

If the time is 6 weeks or more, the 840 mg dose should be re-administered as a 60 minute intravenous infusion followed by the maintenance dose of 420 mg every 3 weeks over 30 to 60 minutes.

Conclusion: The published data results from the NeoSphere and CLEOPATRA provide strong evidence that pertuzumab when used with docetaxel and trastuzumab for HER2-positive breast cancer is superior to trastuzumab and docetaxel alone. The three drug combination can significantly improve pathological complete response rate and prolong progression-free survival. However, there is limited efficacy in the use of pertuzumab as a single-agent. The most frequent adverse events experienced in the pertuzumab groups were diarrhea, rash, febrile neutropenia, dry skin, and vomiting. Based on the effectiveness of pertuzumab when added to docetaxel and trastuzumab during the NeoSphere and CLEOPATRA studies, its use in HER2-positive metastatic breast cancer appears to be clinically useful.

Recommended References:

1. Pertuzumab. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2009. Available at: <http://www.clinicalpharmacology.com> Accessed: October 3, 2012.
2. Pertuzumab. Lexi-Drugs [database online]. Lexi-Comp, Inc; October 3, 2012.
3. Perjeta [package insert]. San Francisco, CA: Genentech, Inc.: 2012.

4. Pertuzumab. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: October 3, 2012.
5. Pertuzumab. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: <http://online.factsandcomparisons.com>. Accessed: October 3, 2012.
6. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, Clark E, Benyunes MC, Ross G, Swain SM; CLEOPATRA Study Group. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *N Engl J Med*. 2012 Jan 12;366(2):109-19
7. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, Clark E, Benyunes MC, Ross G, Swain SM; CLEOPATRA Study Group. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *N Engl J Med*. 2012 Jan 12;366(2):109-19
8. Gianni L, Llado A, Bianchi G, Cortes J, Kellokumpu-Lehtinen P, Cameron D, Miles D, Salvagni S, Wardley A, Goeminne J, Hersberger V, Baselga J. Open-Label, Phase II, Multicenter, Randomized Study of the Efficacy and Safety of Two Dose Levels of Pertuzumab, a Human Epidermal Growth Factor Receptor 2 Dimerization Inhibitor, in Patients with Human Epidermal Growth Factor Receptor2-Negative Metastatic Breast Cancer. *J Clin Oncol*. 2010 Feb;28:1131-1137.

Prepared by: Brittany Linaburg, Doctor of Pharmacy Candidate