Pertuzumab (Perjeta™)

National Drug Monograph

December 2014

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Pertuzumab is a recombinant humanized monoclonal antibody that binds at the HER2 extracellular domain (subdomain II) of the human epidermal growth factor receptor 2 (HER2) protein. Binding at this site prevents HER2 from dimerizing with other ligand-activated HER receptors preventing ligand-initiated intracellular signaling. Pertuzumab is also referred to as a HER2/neu receptor antagonist.
Indication(s) Under Review	• Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. • Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival. Limitations of use: o The safety of pertuzumab as part of a doxorubicin-containing regimen has not been established. o The safety of pertuzumab administered for greater than 6 cycles for early breast cancer has not been established.
Dosage Form(s) Under Review	Pertuzumab 420 mg/14 ml single-use vial for injection
REMS	☐ REMS ☒ No REMS *See Other Considerations for additional REMS information*
Pregnancy Rating	Pregnancy Category D

Executive Summary

Efficacy in Metastatic Breast Cancer (MBC)	• FDA-approval of pertuzumab in MBC was supported by the phase 3 trial (CLEOPATRA) that compared placebo/trastuzumab/docetaxel to pertuzumab/trastuzumab/docetaxel in patients with HER2-positive, locally advanced or metastatic breast cancer who had not received prior chemotherapy or biologic therapy for MBC • The primary endpoint of PFS was greater in the pertuzumab arm. The PFS benefit was consistent whether or not patients received adjuvant or neoadjuvant therapy with trastuzumab. • The Overall Survival (OS) endpoint did not meet statistical significance, but a trend showing improvement favored the pertuzumab arm. Extending the follow-up by one year allowed a statistically significant benefit of OS in the pertuzumab arm to be obtained.

	• ASCO Clinical Practice Guideline recommends the combination of pertuzumab, trastuzumab and a taxane in the first-line MBC setting. This is an evidence-based recommendation supported by CLEOPATRA; Evidence quality is high; Strength of recommendation is strong
Efficacy as Neoadjuvant Treatment	• The FDA granted conditional approval to the combination of pertuzumab with trastuzumab and docetaxel as neoadjuvant therapy in patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer as part of a complete treatment regimen for early breast cancer. • This indication is based on the demonstration of an improvement in pathologic complete response rate. There is currently no data available demonstrating improvement in event-free survival or overall survival. • Results of NeoSphere indicate a pCR rate of 45.8% (95% CI 36.1-55.7) in the pertuzumab, trastuzumab, docetaxel arm which is higher than the other treatment arms with pCR rates of 16.8, 24 and 29%.
Safety	• The most common adverse events (all grades) noted with the combination of pertuzumab, trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash and peripheral neuropathy. Grades 3 - 4 toxicity includes neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia and fatigue. A higher incidence of febrile neutropenia was noted among the Asian population compared to other races. Overall, these events were similar between the MBC and neoadjuvant populations. • Left Ventricular Dysfunction is a concern and LV function should be assessed at baseline and monitored at regular intervals throughout therapy. • Boxed warning: Risk of cardiomyopathy and embryo-fetal toxicity • Infusion-related reactions are possible, so patients should be observed for 60 minutes after the first infusion and for 30 minutes following subsequent infusions.
Other Considerations	**Outcome in clinically significant area**: MBC: Overall Survival 37.6 mos (PBO) vs. not reached (P) Neo: pCR 46% **Effect Size**: MBC: HR 0.66 (0.52-0.84;p=0.0008) Neo: (95% CI 36.1-55.7) **Potential Harms**: MBC: Grade 3 neutropenia (48.9%); all other toxicity < Gr 3 Neo: Grade 3 neutropenia (45%); all other toxicity < Gr 3 **Net Clinical Benefit**: MBC: substantial (high benefit with low risk of harm) Neo: minimal (low benefit with low risk of harm)
Potential Impact	• The combination of pertuzumab, trastuzumab and taxane has changed the standard of care for some patients with MBC. • Patients with HER2-positive MBC who did not receive adjuvant trastuzumab or received adjuvant trastuzumab followed by a treatment-free interval, may be offered the combination of pertuzumab, trastuzumab and taxane as first-line therapy for metastatic disease. • The addition of pertuzumab in the neoadjuvant setting has been shown to increase the pCR, but confirmatory evidence supporting clinical benefit remains to be proven at this point.

Background

Purpose for review

FDA approval of pertuzumab

Issues to be determined:
Does the addition of pertuzumab to first-line therapy of MBC offer advantages to the patient? What about in the neoadjuvant setting?
Should we expect these advantages in our Veteran population?
What safety issues need to be considered?
Does pertuzumab have specific characteristics that are best managed by the non-formulary process, prior authorization or CFU?

Other therapeutic options

Formulary Alternatives	Other Considerations (formulation; disease setting)
Capecitabine	Oral; metastatic
Docetaxel	Injectable; adjuvant; metastatic
Paclitaxel (T)	Injectable; adjuvant; metastatic
Vinorelbine	Injectable; adjuvant; metastatic
Doxorubicin (A)	Injectable; adjuvant
Cyclophosphamide (C)	Injectable; adjuvant; metastatic
Carboplatin	Injectable; adjuvant
Fluorouracil (F)	Injectable; adjuvant
Non-formulary Alternative (if applicable)	**Other Considerations**
Trastuzumab (H)	Injectable; adjuvant; metastatic
Lapatinib	Oral; metastatic
Epirubicin (E)	Injectable; adjuvant

Neoadjuvant/Adjuvant Regimens for HER-2 positive disease	AC-> T + H ± Pertuzumab* TCH ± Pertuzumab* AC -> Docetaxel + H ± Pertuzumab FEC -> Docetaxel + H + Pertuzumab FEC -> Paclitaxel + H + Pertuzumab Paclitaxel + H Pertuzumab + H + Docetaxel -> FEC Pertuzumab + H + Paclitaxel -> FEC EC -> Paclitaxel + H AC -> T + H TCH Docetaxel + H -> FEC
Advanced/MBC Regimens for HER-2 positive disease	Pertuzumab + H + Docetaxel* Pertuzumab + H + Paclitaxel* H ± Paclitaxel ± Carboplatin H ± Docetaxel H ± Vinorelbine H ± Capecitabine Trastuzumab (H) Ado-Trastuzumab emtansine Lapatinib + Capecitabine

* Listed as preferred regimens in NCCN v3.2014

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to October 2014) using the search terms <pertuzumab> and <Perjeta >. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Pertuzumab in Metastatic Breast Cancer (MBC)

Trial	Inclusion Criteria	Interventions	Results
Baselga 2012 CLEOPATRA R, DB, PC, P3 N=808 patients PBO placebo; PTZ pertuzumab; H trastuzumab; D docetaxel	- Locally recurrent, unresectable or metastatic disease; - HER2-positive MBC - No prior chemo or biologic therapy for MBC - ECOG PS 0 or 1 - Adjuvant/neoadjuvant therapy allowed with or without H if ≥ 12 months between end and diagnosis of MBC	PBO/trastuzumab/docetaxel vs. PTZ/trastuzumab/docetaxel Trastuzumab (H) 8 mg/kg IV LD, then 6 mg/kg MD every 3 wks to PD Docetaxel (D) 75 mg/m2 IV q3wks; ↑ 100 mg/m2 if tolerable x 6 cycles PTZ or PBO 840mg IV LD, then 420mg q3wks to PD or toxicity PD based on radiographic, cytologic, photographic evidence or toxic effects	PBO/trastuzumab/docetaxel vs. PTZ/trastuzumab/docetaxel Primary endpoint: PFS PFS 12.4 vs. 18.5 months; HR 0.62(0.51-0.75); p<0.001 Pts (88) who rec'd adj or neoadj chemo w/H: PFS 10.4 vs. 16.9 months; HR 0.62(0.35-1.07) Pt (288) who rec'd adj or neoadj chemo without H: 12.6 vs. 21.6 months; HR 0.60(0.43-0.83)
Swain (2013)[3] CLEOPATRA Overall survival analysis after one additional year of follow-up	Same as above	Same as above	Median follow-up was 30 months; Deaths 37.9 vs. 28.1%; HR 0.66(0.52-0.84;p=0.0008) Median OS 37.6 mos vs. not reached Exploratory subgroup analysis Prior neoadjuvant or adjuvant therapy with H (88 of 808) HR 0.68 (0.30-1.55) indicates OS benefit with pertuzumab
Miles (2013)[5] CLEOPATRA Safety/efficacy analysis in patients > 65 years compared to those younger	Same as above ITT population: 681 (84.3%) age < 65 years; 127 (15.7%) age ≥ 65 years	Same as above	Treatment benefit w/PTZ consistent in all age groups Post hoc analysis, Kaplan-Meier estimates PFS Patients < 65 yrs 12.5 vs. 17.2 mos; HR 0.65(0.53-0.80) Patients ≥ 65 yrs 10.4 vs. 21.6 mos; HR 0.52(0.31-0.86)
Cortes (2013)[6] CLEOPATRA Health-related QOL	Same as above	FACT-B (functional assessment of cancer therapy-breast) questionnaire at baseline & within 3 days prior to each tumor assessment (q9wks) until PD FACT-B comprised of FACT-General and Breast Cancer Subscale (BCS) Trial Outcome Index-Physical/Functional/Breast score (TOI-PFB) is a composite of PWB, FWB and BCS domains	Pre-specified secondary endpoint: Time until decline in HRQoL, defined by ≥ 5 point ↓ from baseline in TOI-PFB ↓ ≥ 5 points in TOI-PFB score 56.7 vs. 59.5% Median time to TOI-PFB ↓ 18.3 vs. 18.4 wks HR.97(0.81-1.16)p=0.716

Metastatic Breast Cancer

- FDA-approval of pertuzumab in MBC was supported by the phase 3 trial (CLEOPATRA) that compared placebo/trastuzumab/docetaxel to pertuzumab/trastuzumab/docetaxel in patients with HER2-positive, locally advanced or metastatic breast cancer who had not received prior chemotherapy or biologic therapy for MBC
- The primary endpoint of PFS was greater in the pertuzumab arm. The PFS benefit was consistent whether or not patients received adjuvant or neoadjuvant therapy with trastuzumab.

- The Overall Survival (OS) endpoint did not meet statistical significance, but a trend showing improvement favored the pertuzumab arm. Extending the follow-up by one year allowed a statistically significant benefit of OS in the pertuzumab arm to be obtained.
- Benefit of PFS was evident in patients, regardless of age (< 65 years and ≥ 65 years).
- Health-related Quality of Life (HRQoL), a secondary endpoint in CLEOPATRA, was similar between placebo and pertuzumab arms with regard to decline in TOI-PFB scores and median time to deterioration of scores.
- ASCO Clinical Practice Guideline recommends the combination of pertuzumab, trastuzumab and a taxane in the first-line MBC setting. This is an evidence-based recommendation supported by CLEOPATRA; Evidence quality is high; Strength of recommendation is strong.[8]
- NCCN Guidelines list the combination of pertuzumab, trastuzumab and taxane as a preferred therapy as first-line therapy of MBC.
- Alternative options for first-line therapy include trastuzumab plus chemotherapy (such as vinorelbine, paclitaxel +/- carboplatin, capecitabine). The pertuzumab combination was compared to trastuzumab and taxane, therefore it is not clear if a similar response would be noted if compared to other trastuzumab-based combinations.

Pertuzumab in Neoadjuvant Therapy of Early Stage Breast Cancer

Trial	Inclusion Criteria	Interventions*	Results
Gianna (2012)[6] NeoSphere R, MC, OL, P2, proof-of-concept study α level 20%	Locally advanced, inflammatory or early HER2-positive breast cancer Operable = T2-3, N0-1, M0; LA = T2-3, N2-3, M0 or T4a-c, any N, M0; Inflamm = T4d, any N, M0 Primary tumor > 2cm Age ≥ 18 yrs; Rec'd no prior cancer tx HER2 IHC 3+ or 2+ ECOG PS 0 or 1; LVEF ≥ 55% via MUGA;	Rand 1:1:1:1 A: H + docetaxel B: pertuzumab + H + docetaxel C: pertuzumab + H D: pertuzumab + docetaxel - Total 4 cycles, then surgery, then arms A, B, D received adjuvant FEC x 3 cycles - Arm C received adjuvant docetaxel x 4 cycles, then FEC x 3 cycles - Trastuzumab continued q3weeks x 1 year in all arms Tumor response (CBE) assessed at each cycle.	Primary endpoint = pathologic CR (pCR) defined as absence of cancer cells at primary tumor site FDA defines as absence of cancer in breast and LN (T0, N0) ITT populations 107 in A, B, D; 96 in C pCR noted in A: 31/107 (29%; 95% CI 20.6-38.5) B: 49/107 (45.8%; 95% CI 36.1-55.7) C: 23/96 (24%; 95% CI 15.8-33.7) D: 18/107 (16.8%; 95% CI 10.3-25.3)
Schneeweiss (2013)[7] MC, OL, P2 TRYPHAENA cardiac safety study	Females ≥ 18 yrs Operable = T2-3, N0-1, M0; LA = T2-3, N2-3, M0 or T4a-c, any N, M0; Inflamm = T4d, any N, M0 Primary tumor > 2cm Age ≥ 18 yrs; Rec'd no prior cancer tx HER2 IHC 3+ or 2+ ECOG PS 0 or 1; LVEF ≥ 55% via MUGA;	Rand 1: 1: 1 Patients randomized to receive 6 neoadjuvant cycles q3wk A: FEC+H+P x3 -> T+H+P x3 B: FEC x3 -> T+H+P x3 C: TCH+P x6 TCH+P T 75mg/m2 (no ↑ allowed) C AUC=6 FEC=5FU+epirubicin+cyclophosphamide 5FU 500mg/m2 Epirubicin 100mg/m2 Cyclophosphamide 600mg/m2	Primary endpoint= evaluate safety & tolerability during neoadjuvant tx; included incidence LVSD ↓ LVEF ≥ 10% points from baseline to < 50% over the course of neoadj tx

	A	B	C
Neoadj (n)	72	75	76
LVSD	4(5.6%)	3(4%)	2(2.6%)
Sx LVSD	0	2(2.7%)	0
LVEF ↓	4(5.6%)	4 (5.3%)	3 (3.9%)
Adjuvant (n)	68	65	67
LVSD	4(5.9%)	5(7.7%)	3 (4.5%)
Sx LVSD	0	0	1(1.5%)
LVEF ↓	4(5.9%)	8(12.3%)	3 (4.5%)
F/U (n)	70	75	74
LVSD	1(1.4%)	2(2.7%)	1(1.4%)
Sx LVSD	0	1(1.3%)	0
LVEF ↓	3(4.3%)	4(5.3%)	2(2.7%)

*Trastuzumab (H) 8mg/kg IV x 1, then 6mg/kg IV every 3 weeks; Pertuzumab (P) 840mg IV x 1, then 420mg IV every 3 weeks; Docetaxel (T) 75mg/m2 IV every 3 weeks (↑ to 100mg/m2 allowed if tolerated); FEC= 5FU 600mg/m2 IV; Epirubicin 90mg/m2 IV; Cyclophosphamide 600mg/m2 IV; Repeat every 3 weeks

Neoadjuvant treatment

- The FDA granted conditional approval to the combination of pertuzumab with trastuzumab and docetaxel as neoadjuvant therapy in patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer as part of a complete treatment regimen for early breast cancer.
- This indication is based on the demonstration of an improvement in pathologic complete response rate. There is currently no data available demonstrating improvement in event-free survival or overall survival. Long-term confirmatory data will be available in the APHINITY trial.
- Results of the TECHNO trial suggest that an endpoint of pCR after neoadjuvant therapy is associated with an improvement in disease-free survival (DFS) and overall survival (OS). Investigations by the German Breast Group indicate that pCR is a valid surrogate endpoint for certain intrinsic breast cancer types (ER/PR-, HER2+, all grades; triple-negative tumors, all grades and ER/PR+, HER2-, grade 3)
- Results of NeoSphere indicate a pCR rate of 45.8% (95% CI 36.1-55.7) in the pertuzumab, trastuzumab, docetaxel arm which is higher than the other treatment arms with pCR rates of 16.8, 24 and 29%.
- Most common adverse events include alopecia, neutropenia, diarrhea, nausea, fatigue, rash and mucosal inflammation. Adverse Events of grade 3 or higher include neutropenia, febrile neutropenia, and leukopenia.

Potential Off-Label Use

The following trials can be found in www.clinicaltrials.gov

- In the first-line MBC setting, pertuzumab is being investigated in combination with other chemotherapy, endocrine and targeted agents. An example is MARIANNE, which is comparing ado-trastuzumab and pertuzumab with ado-trastuzumab and placebo with trastuzumab and a taxane.
- For subsequent MBC treatment, pertuzumab is being investigated in combination with other chemotherapy agents as in PHEREXA, a study of trastuzumab and capecitabine with or without pertuzumab in HER2-positive MBC.
- In the adjuvant setting, the APHINITY trial is researching the addition of pertuzumab to adjuvant therapy that includes chemotherapy with trastuzumab; this trial will also help define the outcomes of the pertuzumab in the neoadjuvant setting.
- The role of pertuzumab is also being investigated in the neoadjuvant and metastatic settings of HER2-Positive Gastroesophageal Junction or Gastric Cancer.

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	Cardiomyopathy – Pertuzumab administration can result in subclinical and clinical cardiac failure. Evaluate left ventricular function in all patients prior to and during treatment with pertuzumab. Discontinue pertuzumab treatment for a confirmed clinically significant decrease in left ventricular function. Embryo-Fetal Toxicity – Exposure to pertuzumab can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception.
Contraindications	Patients with known hypersensitivity to pertuzumab or to any of its excipients
Warnings/Precautions	• Embryo-Fetal Toxicity. Pertuzumab can result in fetal harm if given to a pregnant woman. Pregnancy status should be verified prior to beginning therapy. Patients should be informed of the potential risk of embryo-fetal death, birth defects and need for contraception during and after treatment. If a patient becomes pregnant while receiving pertuzumab, they should be informed of the potential risks

to the fetus. Pregnant patients with exposure to pertuzumab should be reported to the Genentech Adverse Event Line at 1-888-835-2555. Women who may be exposed during pregnancy can be enrolled in the MotHER Pregnancy Registry at 1-800-690-6720. Monitor pregnant patients for oligohydramnios.

- Left Ventricular Dysfunction. In the MBC setting, pertuzumab in combination with trastuzumab and docetaxel was not associated with increases in incidence of symptomatic LVSD or decreases in LVEF compared to placebo in combination with trastuzumab and docetaxel. In the neoadjuvant setting, the incidence of LVSD was higher and an increased incidence of decline in LVEF in the pertuzumab, trastuzumab and docetaxel arm was noted. LVEF should be assessed at baseline and at regular intervals (such as every 3 weeks in the metastatic setting and every 6 weeks in the neoadjuvant setting). If LVEF < 45% or is 45-49% with a 10% absolute decrease below baseline LVEF, hold pertuzumab and trastuzumab and repeat LVEF within ~ 3 weeks.
- Infusion-related Reactions. Pertuzumab has been associated with infusion-related reactions. Common reactions include pyrexia, chills, fatigue, headache, hypersensitivity, asthenia and vomiting. The majority of reactions are Grade 1 or 2 with less than 1% being Grade 3 or 4. Observe patients for 60 minutes following the first infusion and for 30 minutes after subsequent infusions. Should significant reactions occur, slow or interrupt the infusion and provide appropriate medical therapies. Consider permanent discontinuation in cases where patients experience severe infusion-related reactions.
- Hypersensitivity Reactions/Anaphylaxis. Observe patients closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis, has been observed with pertuzumab therapy. Medications to treat such reactions should be available for immediate use. Pertuzumab is contraindicated in patients with known hypersensitivity to pertuzumab or any of its excipients.
- HER2 Testing. Overexpression of HER2protein is necessary for the selection of patients appropriate for pertuzumab therapy, as these were the only patients studied and received benefit from pertuzumab. Evidence of HER2 overexpression was defined as 3+ IHC or FISH amplification ratio $\geq$ 2.0 in the clinical trials. HER2 status should be performed by laboratories proficient in utilizing FDA-approved tests to obtain reliable results.

Safety Considerations

- Metastatic Setting:
  - Grade 3 or higher toxicities included neutropenia, febrile neutropenia, diarrhea and peripheral neuropathy
  - The incidence of all Grades of FN was higher in the Asian population
  - Infection was the most common cause of death due to an adverse event
  - Patients $\geq$ 65 years experienced more diarrhea, fatigue, asthenia, reduced appetite, vomiting and dysgeusia, but less neutropenia

- Neoadjuvant Setting:
  - Events of grade 3 or higher include: neutropenia, febrile neutropenia and leukopenia.
  - The incidence of symptomatic LVSD was low in all treatment arms; a significant decline in LVEF was low as well. Pertuzumab does not appear to increase rate of CV dysfunction in combo with trastuzumab and chemotherapy in the neoadjuvant setting.

Adverse Reactions

Common adverse reactions	**MBC setting with trastuzumab and docetaxel:** Incidence > 30%: diarrhea, alopecia, neutropenia, nausea, fatigue, rash, peripheral neuropathy; Grade 3,4 events > 2%: neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, fatigue. **Neoadjuvant setting with trastuzumab and docetaxel:** Incidence > 30%: alopecia, neutropenia, diarrhea, nausea; Grade 3,4 events > 2%: neutropenia, febrile neutropenia, leukopenia, diarrhea **Neoadjuvant setting with trastuzumab and docetaxel followed by FEC:** Incidence > 30%: diarrhea, nausea, alopecia, neutropenia, vomiting, fatigue; Grade 3,4 events > 2%: neutropenia, leukopenia, febrile neutropenia, diarrhea, LV dysfunction, anemia, dyspnea, nausea, vomiting
Death/Serious adverse reactions	MBC: Infection was the most common cause of death
Discontinuations due to adverse reactions	MBC: Death due to adverse events: 2% (vs. 2.5% in placebo arm)

Drug Interactions

Drug-Drug Interactions

- No drug-drug interactions were observed between pertuzumab and trastuzumab or pertuzumab and docetaxel.
- Cardiotoxicity is a concern with trastuzumab and anthracycline-derivative cytotoxic agents therefore there is a theoretical concern that drugs toxic to myocardial tissues could have an additive effect.

Risk Evaluation

As of October 10, 2014

	Comments
Sentinel event advisories	• None Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	• Pertuzumab: trastuzumab, ado-trastuzumab emtansine, panitumumab • Perjeta: Pazopanib, Ponatinib, Pexeva, Provera, Provigil, Jetrea Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer and latest update of National Comprehensive Cancer Network (NCCN) Guidelines include pertuzumab in their treatment recommendations for MBC. Cost analyses are not considered in either Guideline.
- Upon initial review in August 2013, National Institute for Health and Care Excellence (NICE) reviewers did not find the pertuzumab combination to be cost-effective in the advanced breast cancer setting. In June 2014, the NICE Decision Support Unit (DSU) was asked to formulate a discussion paper to aid in assessing technologies that are not cost effective. The NICE Guidance Executive team will defer any decision on pertuzumab with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer until the discussion paper is complete.
- The Pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends funding for the combination of pertuzumab, trastuzumab and a taxane conditional on cost-effectiveness being improved to an acceptable level. Funding will be designated for the palliative treatment of HER2-positive patients that meet certain criterion.

Outcome in clinically significant area	MBC: Overall Survival 37.6 mos (PBO) vs. not reached (P) Neo: pCR 46%
Effect Size	MBC: HR 0.66 (0.52-0.84;p=0.0008) Neo: (95% CI 36.1-55.7)
Potential Harms	MBC: Grade 3 neutropenia (48.9%); all other toxicity < Gr 3 Neo: Grade 3 neutropenia (45%); all other toxicity < Gr 3
Net Clinical Benefit	MBC: significant (high benefit with low risk of harm) Neo: minimal (low benefit with low risk of harm)

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life
Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio
Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)
Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

- Refer to the package insert for full dosing information.

Special Populations (Adults)

	Comments
Elderly	• Overall, no differences in efficacy or safety of pertuzumab in elderly compared to younger patients have been noted; a population pharmacokinetic analysis notes no significant difference was observed in patients < 65 years and patients ≥ 65 years.
Pregnancy	• There are no adequate and well-controlled studies of pertuzumab in pregnant women. Animal studies indicate that fetal harm can result. If pertuzumab is given during pregnancy or if patient becomes pregnant while receiving pertuzumab, the patient should be informed of the potential risk to the fetus. • Females of childbearing potential should be advised to use effective contraception during and 6-months following the last dose of pertuzumab.
Lactation	• It is unknown if pertuzumab is excreted in human milk, but

		human IgG is, therefore a potential risk of serious adverse reaction exists in nursing infants; a decision to discontinue breastfeeding or discontinue the drug should be made given the drug half-life and importance of pertuzumab to the mother.
Renal Impairment	•	No dose adjustments are need in patients with mild (60-90 ml/min) or moderate (30-60 ml/min) renal impairment; no dose adjustment can be recommended in severe renal impairment (CrCl < 30 ml/min) because of limited data.
Hepatic Impairment	•	No studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab
Pharmacogenetics/genomics	•	No data identified

Projected Place in Therapy

- Approximately 200,000 new cases of breast cancer are expected to be diagnosed each year with about 40,000 deaths. Metastatic breast cancer is the initial diagnosis in ~ 5% of the population, while ~30% of those with early stage breast cancer will at some point, develop metastatic disease.
- It is estimated that 15-20% of patients with breast cancer have HER2-overexpression.

First-line therapy of HER2-positive Metastatic Breast Cancer (MBC) in combination with trastuzumab and docetaxel

- The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer and latest update of National Comprehensive Cancer Network (NCCN) Guidelines include pertuzumab in their treatment recommendations for MBC.
- Pertuzumab, in combination with trastuzumab and a taxane , has a potential role as first-line therapy in the MBC setting.
- CLEOPATRA was a double-blind, randomized, placebo-controlled phase 3 trial comparing the combination of pertuzumab, trastuzumab, docetaxel to placebo, trastuzumab, docetaxel.
- Evidence GRADE. Evidence quality: high; strength of recommendation: strong
- The pertuzumab combination (pertuzumab/trastuzumab/taxane) would replace a current combination of trastuzumab (non-formulary) and cytotoxic chemotherapy in the first-line MBC setting.

Neoadjuvant therapy of HER2-positive, locally advanced, inflammatory or early stage breast cancer, in combination with trastuzumab and docetaxel

- The FDA-approval in the neoadjuvant setting is based upon an improvement in pathological complete response rate. Evidence in improvement of clinical outcomes such as event-free survival or overall survival has not been demonstrated.
- Although mature data regarding clinical outcomes with the pertuzumab combination is not yet available, data supporting positive outcomes (improved EFS, improved OS) when pCR is used as a surrogate endpoint in the neoadjuvant setting is available.
- As the optimal neoadjuvant treatment regimen has not been defined, it is unclear if the benefit of pertuzumab would be expected when added to other neoadjuvant regimens; some question if the treatment arms in NeoSphere were appropriate to make comparisons.

References

Perjeta [prescribing information]. South San Francisco, CA: Genentech, Inc; September 2013.

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Appendix 1: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

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