Corporate Medical Policy

Pertuzumab for Treatment of Malignancies

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Description of Procedure or Service

Pertuzumab (Perjeta™) is a monoclonal antibody that is a human epidermal growth factor receptor 2 (HER2) antagonist. It has received U.S. Food and Drug Administration (FDA) approval for use in combination with trastuzumab and docetaxel for the treatment of HER2-positive, metastatic breast cancer; as neoadjuvant treatment of HER2-positive locally advanced, inflammatory, or early-stage breast cancer; and as adjuvant treatment of *HER2*-positive early breast cancer at high risk of recurrence. The combination of 2 HER2-active agents targeting different subdomains of HER2 may result in a more comprehensive blockade of HER2 and its pathways, and thus may lead to a greater treatment effect.

Background

HER2-positive breast cancer is a breast cancer that tests positive for a protein called human epidermal growth factor receptor 2 (HER2)**,** which promotes the growth of cancer cells. With too many HER2 proteins, the cancer cells multiply fast. IHC (immunohistochemistry) is the test used to count the number of HER2 receptors. Cancer cells with more than two *HER2* gene copies or too many HER2 receptors are called "HER2 positive."

Description of Disease.

Breast cancer accounts for nearly 1 in 3 cancer diagnoses in women in the U.S. Among women, it is the most common cancer after non-melanoma skin cancer. After lung cancer, breast cancer ranks second for cancer mortality. In 2013, an estimated 232,000 new cases of invasive breast cancer were diagnosed among women, and approximately 40,000 women are expected to die from breast cancer.

Metastatic Breast Cancer

Metastatic breast cancer has a poor prognosis. In a cohort of 3,524 women with de novo Stage IV or relapsed breast cancer diagnosed between 1992 and 2007, the median overall survival was 39.2 months among patients with de novo Stage IV and 27.2 months among patients with relapsed disease (estimates independent of HER2 status). Factors associated with reduced survival for patients with metastatic breast cancer include age ≥50 years, visceral disease, shorter disease-free interval, negative hormone receptor status, and HER2-positive status.

Systemic treatment for metastatic breast cancer is mainly palliative. The goals of treatment are to prolong survival, alleviate symptoms, and maintain or improve quality of life. Treatment is primarily with chemotherapeutic and other anti-tumor drugs. The National Comprehensive Cancer Network (NCCN) guidelines on treatment of metastatic breast cancer include specific recommendations for first-line treatment of HER2-positive metastatic breast cancer. All of the recommended treatment regimens in the guidelines include trastuzumab. Recommended agents that are used singly or in combination with trastuzumab are paclitaxel, docetaxel, vinorelbine, capecitabine, and carboplatin.

Locally Advanced, Inflammatory and Early-stage Breast Cancer

Treatment for operable (locally invasive or early-stage) breast cancer includes surgery and/or radiotherapy followed by adjuvant chemotherapy to reduce recurrence risk. Since the advent of treatments targeting the *HER2* gene, outcomes for women with early-stage *HER2*-positive breast cancer have improved considerably. Among women with positive lymph nodes who are treated with chemotherapy plus trastuzumab, relapse-free survival now exceeds 80%. Current NCCN guidelines indicate that preoperative (neoadjuvant) chemotherapy may be appropriate for large tumors (>2 cm) in women with invasive breast cancer who are eligible for breast-conserving surgery. Although breast conservation rates are higher after neoadjuvant chemotherapy, a survival advantage has not been shown compared with adjuvant (postoperative) chemotherapy.

Inflammatory breast cancer is a rare, aggressive breast cancer that accounts for 1% to 6% of U.S. breast cancer cases. Inflammatory breast cancer is characterized by erythema and edema of the skin (peau d'orange) that has a palpable border and is commonly hormone receptor–negative and *HER2*-positive. Based on retrospective and prospective studies, current NCCN guidelines recommend preoperative chemotherapy with an anthracycline-based regimen (eg, doxorubicin plus cyclophosphamide followed by a taxane). For patients with *HER2*-positive disease, NCCN recommends adding trastuzumab for up to 1 year.

HER2 Protein

HER2, previously called HER2/neu, or ErbB-2, is part of the HER tyrosine kinase receptor family that includes 4 transmembrane receptors (HER1 [EGFR], HER2, HER3, and HER4). These receptors mediate tumor cell growth, survival, and differentiation. The HER receptors, when activated by extracellular ligand binding, dimerize and activate cell signaling through the phosphatidyl inositol-3 (PI3)-kinase/AKT pathway, which regulates tumor cell survival, to and through the mitogen-activated protein kinase (MAPK) pathway, which regulates cellular proliferation. HER2 has no known ligand; it forms active heterodimers (particularly HER2:HER3) and, when overexpressed, homodimers (HER2:HER2) and that initiate tyrosine kinase signaling.

Approximately 20-25% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2), a transmembrane glycoprotein receptor with tyrosine kinase activity. Overexpression of this receptor is associated with reduced time to disease recurrence and poorer prognosis. Prior to the advent of HER2 targeted therapy, HER2 overexpression was associated with shorter disease-free and overall survival than women with either lymph node-negative or lymph node-positive breast cancers, with lack of responsiveness to tamoxifen therapy, and with altered responsiveness to cytotoxic chemotherapy.

Regulatory Status

Pertuzumab (Perjeta™) received U.S. Food and Drug Administration (FDA) approval for metastatic breast cancer in June 2012. Labeled indications are for use in combination with trastuzumab and docetaxel for the treatment of patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. In September 2013, pertuzumab was granted accelerated approval by the FDA for neoadjuvant treatment of breast cancer.

Labeled indications are for:
"use in combination with trastuzumab and docetaxel in patients with *HER2*-positive, locally advanced, inflammatory, or early-stage breast cancer (either >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 pathologic complete response rate. No data are available demonstrating improvement in event-free survival or OS [overall survival].

Limitations of use:

- The safety of pertuzumab as part of a doxorubicin-containing regimen has not been established.
- The safety of pertuzumab administered for greater than 6 cycles for early breast cancer has not been established.

Data from the phase 3 APHINITY trial (expected in 2023) are required to convert accelerated approval for this indication to full approval.

Related Policies
Trastuzumab (Herceptin®) and Trastuzumab Biosimilars

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for pertuzumab for treatment of malignancies when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Pertuzumab for Treatment of Malignancies is covered

The use of pertuzumab may be considered medically necessary in the treatment of HER2-positive breast cancer when the following conditions are met:

- neoadjuvant treatment of locally advanced, inflammatory, or early stage breast cancer (> 2cm in diameter or node-positive); **OR**
- treatment of metastatic breast cancer if pertuzumab was not previously administered; **OR**
- adjuvant treatment of early breast cancer at high risk of recurrence; **AND**
- pertuzumab is used in combination with trastuzumab, a taxane, with or without carboplatin.

Use of Pertuzumab may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**

- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached

When Pertuzumab for Treatment of Malignancies is not covered

The use of pertuzumab is investigational for all other indications, including but not limited to HER2-positive gastric, colorectal, non-small cell lung, and ovarian cancers, HER2-positive cancers of the gastro-esophageal junction; and HER2 negative cancers.

Pertuzumab is considered investigational when used for:

1. Non-cancer indications; **OR**
2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under "When Pertuzumab is covered."

Policy Guidelines

Pertuzumab (Perjeta®) is a monoclonal antibody that is a human epidermal growth factor receptor 2 (*HER2*) antagonist. It is approved by the U.S. Food and Drug Administration (FDA) in combination with trastuzumab and docetaxel for: (1) treatment of *HER2*-positive, metastatic breast cancer; (2) as neoadjuvant treatment of *HER2*-positive locally advanced, inflammatory, or early stage breast cancer; and (3) as adjuvant treatment of *HER2*-positive early breast cancer at high risk of recurrence. The combination of 2 *HER2*-active agents targeting different subdomains of *HER2* (pertuzumab targets subdomain II and trastuzumab targets subdomain IV) may result in a more comprehensive blockade of HER2 and its pathways, and thus may lead to greater treatment effect.

The safety of pertuzumab administered for greater than 6 cycles for early breast cancer in the neoadjuvant setting has not been established.

Pertuzumab has shown fetotoxicity in animal studies. Women of childbearing age should be on effective contraception prior to starting pertuzumab.

The use of pertuzumab may be associated with LV (left ventricular) dysfunction, similar to trastuzumab. The CLEOPATRA trial had the following inclusion criteria and recommendations for monitoring:

- LV ejection fraction >50% at start of therapy
- If LVEF decreases to 45% to 49% with a 10% greater decrease below pretreatment values, or if LVEF decreases to less than 45%, both pertuzumab and trastuzumab should be withheld for at least 3 weeks. If the LV ejection fraction does not improve or continues to decline after 3 weeks of holding the drugs, both pertuzumab and trastuzumab should be discontinued.

For individuals who have *HER2*-positive, locally recurrent or metastatic breast cancer who receive pertuzumab in combination with trastuzumab and a taxane, the evidence includes 1 randomized controlled trial (RCT). Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortailty and moribidity. The RCT compared pertuzumab plus docetaxel and trastuzumab with docetaxel and trastuzumab alone, and reported a statistically significant 6.1-month improvement in progression-free survival for the pertuzumab group. There was a 9.8% absolute difference in overall survival, a statistically and clinically significant result. Adverse events occurring more commonly in the pertuzumab group were diarrhea, rash, mucosal inflammation, neutropenia, febrile neutropenia, and dry skin. These trial results indicate a strong likelihood that health outcomes are improved when pertuzumab is added to standard treatment for locally recurrent or metastatic breast cancer. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have *HER2*-positive, locally advanced, inflammatory, or early-stage operable breast cancer who receive pertuzumab in combination with trastuzumab and a taxane, the evidence includes includes 1 RCT. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortailty and moribidity. The NeoSphere pivotal trial supported efficacy of pertuzumab in the neoadjuvant setting using a surrogate outcome (pathologic complete response [pCR]); the validity of pCR as a surrogate for survival outcomes was deemed reasonable. In NeoSphere, there was a 17.8% absolute difference in pCR for the pertuzumab group, a statistically significant difference. In stratified analysis, treatment effect was greater for hormone receptor–negative patients (24.6% absolute difference) versus hormone receptor–positive patients (10.0% absolute difference). Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have *HER2*-positive early-stage breast cancer who receive postoperative pertuzumab in combination with trastuzumab and a taxane (adjuvant therapy), the evidence includes an RCT. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Eligible patients for the APHINITY trial had either node-positive disease or node-negative disease with tumor diameter greater than 1.0 cm. Node-negative patients with tumor diameter between 0.5 and 1.0 cm were initially eligible if at least one high-risk factor (i.e. histological or nuclear grade 3, estrogen/progesterone receptor negativity, or age less than 35 years) was present; however, a later protocol amendment no longer included node-negative disease within patient eligibility. Although the large adequately powered APHINITY trial, which randomized 4805 patients with a median follow-up of 45 months, met its statistically significant threshold for the primary end point of invasive disease-free survival in favor of pertuzumab, the effect size was small, with an absolute decrease of 0.9 percentage points in the rate of recurrence or death at 3 years; the upper bound of confidence interval of the hazard ratio included 1. Further, the trial showed no statistically significant improvement in overall survival with pertuzumab compared with control. While the safety analysis showed a consistently increased incidence of adverse events in the pertuzumab arm vs the placebo arm, the differences were small and not statistically significant, except for the incidence of diarrhea. However, the safety analysis was biased in favor of pertuzumab arm, because the patients in whom cardiac toxicity from anthracycline treatment precluded *HER2*-targeted treatment in the pertuzumab arm were excluded from the analysis, while toxic effects were reported in their entirety for all patients randomized to placebo. On average, 62.5 patients would have to receive pertuzumab treatment instead of standard of care for one additional patient not to have any invasive disease event while, on average, 14.5 patients would have to receive pertuzumab instead of standard of care for one additional patient to have an adverse event greater than grade 3. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have *HER2*-positive non-breast cancer malignancies who receive pertuzumab, the evidence includes RCTs, uncontrolled trials and case series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The phase 3 PENELOPE trial found that adding pertuzumab to chemotherapy did not significantly improve progression-free survival in patients with platinum-resistant ovarian carcinoma. The evidence is insufficient to determine the effects of the technology on health outcomes.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), "Investigational (Experimental) Services."

Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: *J9306, S0353, S0354*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.20, 12/13/2012

Senior Medical Director – 1/2013

Specialty Matched Consultant Panel – 4/2013

Specialty Matched Consultant Panel – 4/2014

US Food and Drug Administration. FDA approves Perjeta for neoadjuvant breast cancer treatment. Accessed 4/30/2014 from http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm370393.htm

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.20, 5/22/2014

Specialty Matched Consultant Advisory Panel- 4/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.20, 5/21/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.20, 10/15/2015

Specialty Matched Consultant Advisory Panel- 4/2016

Medical Director review 5/2016

Medical Director review 10/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.20, 10/13/2016

Medical Director review 3/2017

Specialty Matched Consultant Advisory Panel- 4/2017

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: breast cancer. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed June 7, 2017.

http://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.20, 10/12/2017

U.S. Food and Drug Administration. FDA grants regular approval to pertuzumab for adjuvant treatment of HER2-positive breast cancer. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm590005.htm. Accessed March 29, 2018.

Perjeta (pertuzumab) [prescribing information]. South San Francisco, CA: Genentech Inc; December 2017. Available at: https://www.gene.com/download/pdf/perjeta_prescribing.pdf. Accessed March 29, 2018.

Specialty Matched Consultant Advisory Panel- 4/2018

Medical Director review 6/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.20, 10/10/2018

Specialty Matched Consultant Advisory Panel- 4/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.20, 10/17/2019

Policy Implementation/Update Information

2/12/13 New Evidence Based Guideline. "The use of pertuzumab may be appropriate in the treatment of breast cancer when all of the following conditions are met: Patient has HER2–positive metastatic breast cancer and Pertuzumab is used in combination with trastuzumab and a taxane (e.g., docetaxel, paclitaxel)." "The use of pertuzumab is not recommended for all other indications, including but not limited to locally advanced breast cancer, local recurrences of breast cancer following treatment, HER2-positive gastric cancers, and HER2-positive cancers of the gastro-esophageal junction." Senior Medical Director review 1/15/13. (btw)

5/14/13 Specialty Matched Consultant Panel review 4/17/2013. Changed Table 1, Positive Results from "Ratio of HER2 /CEP17 is >2.2." to "Ratio of HER2 /CEP17 is > or equal to 2.0". (btw)

11/26/13 Changed the range for Equivocal in Table 1. Testing for HER2 Overexpression and/or Amplification in the Description section from "Ratio of HER2/CEP 17 is between 1.8 and 2.2" to "Ratio of HER2/CEP 17 is between 1.8 and 2.0" based on Specialty Matched Consultant review. (btw)

12/31/13 Added 2014 HCPCS code, J9306, to Billing/Coding section. Deleted HCPCS code C9292. (btw)

5/13/14 Specialty Matched Consultant Panel review 4/26/2014. Added "neoadjuvant breast cancer" to the Evidence Based Guideline section. (btw)

5/26/15 Evidence based guideline converted to corporate medical policy. Medical director review. Specialty Matched Consultant Panel review 4/2015. Reference added. Notification given 5/26/15 for effective date 7/28/15. (lpr)

11/24/15 Reference added. No change to policy statement. (lpr)

5/31/16 Description and Policy Guidelines sections revised and updated. Under When Covered: added covered indication for "treatment of locally advanced, inflammatory, or early stage (either >2 cm in diameter or node positive) breast cancer." Revised Table 1.for clarity. Specialty Matched Consultant Advisory Panel review 4/27/2016. Medical Director review 5/2016. (lpr)

12/30/16 Updated Description section extensively and removed Table 1. Updated Policy Guidelines section. Medical Director review 10/2016. No change to policy statement. Reference added. Added HCPCS codes S03653, S0354 to Billing/Coding section. Notification given 12/30/16 for effective date 4/1/17. (lpr)

5/26/17 Added the following statement to "When Covered" section: "Use of Pertuzumab may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached". Under "When Not Covered" section, added the statement "Pertuzumab is considered investigational when used for: 1)Non-cancer indications; **OR** 2) When criteria are not met regarding FDA labeling **OR** strong

endorsement/ support by nationally recognized compendia, as stated under "When Pertuzumab is covered." Added the following statements under "Policy Guidelines" section: 1)Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services." 2) Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia. Medical director review 3/2017. Specialty Matched Consultant Advisory Panel review 4/26/2017. No change to policy statement. (lpr)

6/30/17 Under Description section added definition for HER2 disease. Under "When Covered" section changed **OR** to **AND** under the second bullet for HER2 positive disease; added carboplatin to combination of drugs; clarified the 6 cycle limit of pertuzumab with use in neoadjuvant treatment and added stage classification. References added. (lpr)

12/15/17 Reference added. (lpr)

7/13/18 Added the following statement to "When Covered" section: "adjuvant treatment of early breast cancer at high risk of recurrence; **AND**," added "**OR**" after statement "treatment of metastatic breast cancer if pertuzumab was not previously administered," and added "treatment of locally advanced, inflammatory, or early stage" for clarity related to neoadjuvant treatment indication. Updated "Description of Procedure or Service" and "Policy Guidelines" sections to include approved indications listed in "When Covered" section and additional clinical trial data for adjuvant treatment of breast cancer at high risk of recurrence. References added. Specialty Matched Consultant Advisory Panel review 4/25/2018. Medical Director review 6/2018. (krc)

4/30/19 Reference added. Specialty Matched Consultant Advisory Panel review 4/17/2019. No change to policy statements. (krc)

6/9/20 Reference added. Specialty Matched Consultant Advisory Panel review 4/15/2020. No change to policy statements. (krc)