Medical Drug Clinical Criteria

Subject:	Perjeta (pertuzumab)		
Document #:	CC-0110	**Publish Date:**	04/01/2025
Status:	Revised	**Last Review Date:**	02/21/2025

Table of Contents

Overview

This document addresses the use of Perjeta (pertuzumab), a recombinant humanized monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) protein. Perjeta interrupts the communication pathway involved in the growth and progression of the cancer cells in the tumor.

The FDA approved indications for Perjeta include for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Perjeta is also FDA approved for use in combination with trastuzumab and chemotherapy for:

- The 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
- The adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence

The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Perjeta in the adjuvant setting if a regimen containing pertuzumab was not used as neoadjuvant therapy, with support based on an extrapolation of evidence from treatment (CLEOPATRA trial) in participants with metastatic disease and improvements in pathological complete response in the neoadjuvant setting. Pertuzumab plus trastuzumab in combination with paclitaxel is an NCCN category 2A recommendation. Additionally, NCCN recommends “for patients with disease progression after treatment with trastuzumab-based therapy without pertuzumab, a line of therapy containing both trastuzumab plus pertuzumab with or without a cytotoxic agent (such as vinorelbine or taxane) may be considered.” Also, specialty consensus opinion suggests that pertuzumab in combination with trastuzumab and docetaxel or paclitaxel may be used in a single line of therapy for metastatic disease.

The NCCN Panel notes that FDA-approved biosimilars may be substituted for trastuzumab wherever the therapy is recommended within their guidelines.

Multiple phase 2 clinical trials are currently evaluating the use of pertuzumab as a treatment for other solid tumors (for example, colorectal cancer, head and neck cancers, neuroendocrine tumors, non-small cell lung cancer, prostate cancer, and rectal cancer) and in combination with other drugs and targeted therapies. However, the data demonstrating safety and efficacy from these trials have not been published and only their abstracts are available (Gupta R et.al. 2020, Meric-Bernstam F, et. al. 2019, Javie M. et.al. 2021, NCT03225937).

As a result of clinical trials demonstrating the effectiveness of pertuzumab with chemotherapy, additional clinical trials are studying the efficacy of adding pertuzumab to specific targeted biologic agents and/or with other chemotherapy agents. However, at this time, there is no evidence to support the safety and efficacy of combining pertuzumab with other biologic agents not discussed above.

Additionally, investigators continue to study the prevalence and role of anti-HER2 therapy in other malignancies. However, there have been no large randomized controlled trials to draw reasonable conclusions regarding the safety and efficacy of pertuzumab versus current standard therapies for malignancies other than breast cancers.

Perjeta has a black box warning for Left Ventricular Dysfunction and Embryo-Fetal Toxicity. Perjeta can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Exposure to Perjeta can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception.

Definitions and Measures

Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

Disease Progression: Cancer that continues to grow or spread.

American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) developed joint guideline recommendations for HER2 testing in breast cancer and the guideline was updated in 2013. NCCN guidelines for breast cancer (2019) have incorporated the updated ASCO/CAP recommendations for HER2 status into the treatment algorithms for HER2 targeted therapy

Positive HER2:

- IHC 3+ based on circumferential membrane staining that is complete, intense. (Observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells).
- ISH positive based on:
    - Single-probe average HER2 copy number ≥ 6.0 signals/cell*.
    - Dual-probe HER2/CEP 17 ratio ≥ 2.0* with an average HER2 copy number ≥ 4.0 signals/cell.
    - Dual-probe HER2/CEP17 ratio ≥ 2.0* with an average HER2 copy number < 4.0 signals/cell.
    - Dual-probe HER2/CEP17 ratio < 2.0* with an average HER2 copy number ≥ 6.0 signals/cell.
      *(Observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells, by counting at least 20 cells within the area)

Equivocal HER2:

- IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within ≤10% of the invasive tumor cells.
- ISH equivocal based on:
    - Single-probe average HER2 copy number ≥ 4.0 and < 6.0 signals/cell.
    - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number ≥ 4.0 signals/cell.

Negative HER2 if a single test (or both tests) performed show:

- IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells.
- IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells.
- ISH negative based on:
    - Single-probe average HER2 copy number < 4.0 signals/cell.
    - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell.

Hormonal therapy: Treatment that adds, blocks, or removes hormones. Agents that slow or stop the growth of certain cancers, synthetic hormones or other drugs may be given to block the body's natural hormones.

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.

Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

Primary refractory disease: Cancer that does not respond at the beginning of treatment; may also be called resistant disease.

Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.

Targeted biologic agent: A newer type of drug developed specifically to target genetic changes in cells that cause cancer. It works differently than standard chemotherapy drugs, often with different side effects.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Perjeta (pertuzumab)

Requests for Perjeta (pertuzumab) may be approved if the following criteria are met:

I. Individual has a diagnosis of HER2-positive (HER2+) breast cancer (NCCN 2A); **AND**
   A. Confirmed by *one* of the following:
      1. Immunohistochemistry (IHC) is 3+;
         OR
      2. In situ hybridization (ISH) positive;

   AND
   B. Individual is using in one of the following ways:
      1. Individual has a diagnosis of recurrent unresectable or metastatic breast cancer (Label, NCCN 1, 2A); **AND**
         a. Individual is using as first-line therapy in combination with trastuzumab (or trastuzumab biosimilars) and either docetaxel or paclitaxel;
            OR
         b. Pertuzumab may be considered for disease progression in combination with trastuzumab (or its biosimilars), with or without cytotoxic therapy (eg, vinorelbine or taxane) for one line of therapy in those previously treated with chemotherapy and trastuzumab (or trastuzumab biosimilars) without pertuzumab;

      OR
      2. Individual has early stage, locally advanced, or inflammatory breast cancer (Label, NCCN 2A); **AND**
         a. Individual will use in one of the following ways:
            i. Neoadjuvant (prior to surgery) therapy;
               AND
            ii. The primary tumor is larger than 2 cm in diameter or individual is lymph node positive (clinically evident by palpation or imaging);
               OR
            iii. Adjuvant systemic therapy;
               AND
            iv. The cancer is at high risk of recurrence;

         AND
         b. Individual has a ECOG performance status of 0-2; **AND**
         c. Individual is using in combination with trastuzumab (or trastuzumab biosimilars) and either of the following (Label, NCCN 2A):
            i. Docetaxel with or without carboplatin;
               OR
            ii. Paclitaxel;

         AND
         d. Individual is using pertuzumab for a maximum of 18 cycles (12 month course) (NCCN 2A);

   OR
   C. Individual is requesting Perjeta in combination with trastuzumab (or its biosimilars) for 12 months after completing 6 cycles (18 weeks) of TCHP (docetaxel, carboplatin, trastuzumab (or trastuzumab biosimilars), pertuzumab) for early stage, locally advance, or inflammatory breast cancer (NCCN 2A);

   OR
   D. Individual has metastatic breast cancer with brain metastases and the following criteria are met (NCCN 2A); **AND**
      1. Individual has a primary diagnosis of HER2+ breast cancer; **AND**
      2. Used in one of the following ways:
         a. In those with asymptomatic brain metastases as primary or initial therapy;
            OR
         b. In those with recurrent or stable disease;

      AND
      3. Individual is using in combination with trastuzumab (or trastuzumab biosimilars);

OR

II. Individual has a diagnosis of biliary tract cancer (extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, or gallbladder cancer) (NCCN 2A); **AND**
   A. Individual is using as subsequent treatment in combination with trastuzumab (or trastuzumab biosimilars); **AND**
   B. Individual is using in one of the following ways:
      1. For progression on or after systemic treatment for unresectable or resected gross residual (R2) disease; **OR**
      2. Metastatic disease that is HER2-positive;

OR

III. Individual has a diagnosis of colon or rectal cancer, including appendiceal carcinoma (NCCN 2A); **AND**
   A. Individual is using in one of the following ways:

1. As initial systemic therapy in combination with trastuzumab (or its trastuzumab) if intensive therapy not recommended; **AND**
    a. No prior treatment with a HER2 inhibitor; **AND**
    b. One of the following:
        i. For advanced or metastatic disease proficient mismatch repair/microsatellite-stable (pMMR/MSS); **OR**
        ii. Ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) and HER2-amplified and RAS and BRAF wild-type disease;

    OR
2. As subsequent therapy in combination with trastuzumab (or trastuzumab biosimilars); **AND**
    a. For HER2-amplified and RAS and BRAF wild-type pMMR/MSS disease; **OR**
    b. Ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H if intensive therapy not recommended and no prior treatment with a HER2 inhibitor;

    OR
3. As initial treatment in combination with trastuzumab (or trastuzumab biosimilars); **AND**
    a. For HER2-amplifed and RAS and BRAF wild-type pMMR/MSS only; **AND**
    b. Has unresectable metachronous metastases disease; **AND**
    c. Prior FOLFOX or CapeOX usage within the past 12 months;

OR

IV. Individual has a diagnosis of HER2-positive recurrent salivary gland tumor (NCCN 2A); **AND**
    A. Individual is using as systemic therapy in combination with trastuzumab (or trastuzumab biosimilars); **AND**
    B. With no surgery or radiation therapy option;

OR

V. Individual has a diagnosis of metastatic HER2+ breast cancer with brain metastases (NCCN 2A); **AND**
    A. Individual has a primary diagnosis of HER2 + breast cancer; **AND**
    B. Individual is using in combination with high dose trastuzumab (or trastuzumab biosimilars); **AND**
    C. Using in one of the following ways:
        1. In those with asymptomatic brain metastases as primary or initial therapy; **OR**
        2. In those with stable brain metastases disease in relapsed/recurrent disease.

Requests for Perjeta (pertuzumab) may not be approved for the following:

I. If pertuzumab is administered after trastuzumab (or trastuzumab biosimilars) is discontinued or as part of a regimen without trastuzumab (or trastuzumab biosimilars); **OR**
II. Concomitant use of pertuzumab with other targeted biologic agents not otherwise noted in the criteria above (including, but not limited to erlotinib, cetuximab, panitumumab, bevacizumab (and bevacizumab biosimilars), lapatinib, and ziv-aflibercept); **OR**
III. When the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9306	Injection, pertuzumab, 1 mg [Perjeta]

ICD-10 Diagnosis

C06.9	Malignant neoplasm of mouth, unspecified [malignant neoplasm of minor salivary gland, unspecified site]
C07	Malignant neoplasm of parotid gland
C08.0-C08.9	Malignant neoplasm of other and unspecified major salivary gland
C18.0-C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.1	Intrahepatic bile duct carcinoma

C23	Malignant neoplasm of gallbladder
C24.0-C24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C50.011-C50.929	Malignant neoplasm of breast
C79.31	Secondary malignant neoplasm of brain
C79.81	Secondary malignant neoplasm of breast
Z85.3	Personal history of malignant neoplasm of breast

Document History

Revised: 02/21/2025
Document History:

- 02/21/2025 – Annual Review: Clarify criteria for NCCN 2A breast cancer recommendations in first-line therapy for use in recurrent unresectable disease in addition to metastatic. Add NCCN category 2A recommendation for use in appendiceal carcinoma with colorectal cancer criteria. Add NCCN category 2A criteria for use in CNS cancer when the primary diagnosis is HER2 + breast cancer. Wording and formatting updates. Coding Reviewed: Added ICD-10-CM C06.9, C07, C19, C20, C21.8, C22.1, C23, C79.31. Updated description for C08.0-C08.9 and C24.0-C24.9. Removed ICD-10-CM D05.00-D05.92 and Z17.0.
- 02/23/2024 – Annual Review: Clarify existing NCCN 2A criteria for breast cancer in first-line therapy and progression. Add NCCN category 2A recommendation for use in biliary tract cancers. Add NCCN category 2A criteria for use in colon or rectal cancer. Add NCCN category 2A criteria for use in salivary gland tumors. Wording and formatting updates. Coding Reviewed: Added ICD-10-CM C08.0-C08.9, C18.0-C18.9, C24.0-C24.9.
- 12/11/2023 – Select Review: Update existing criteria for use in metastatic breast cancer following chemotherapy and trastuzumab. Coding Reviewed: No changes.
- 02/24/2023 – Annual Review. Update existing criteria for use in breast cancer to clarify neoadjuvant and adjuvant use. Add 2A recommendation from NCCN for use in brain metastases with HER2+ metastatic breast cancer. Coding Reviewed: No changes.
- 02/25/2022 – Annual Review: Update Perjeta criteria for use after TCHP cycle. Update criteria to ensure pertuzumab and trastuzumab therapy continues if paclitaxel or docetaxel is contraindicated/discontinued for metastatic breast cancer. Minor wording and formatting updates. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: Update Perjeta criteria with clarifying language. Coding Reviewed: Added ICD-10-CM Z17.0.
- 02/21/2020– Annual Review: Update Perjeta criteria with clarification for use with trastuzumab or trastuzumab biosimilars. Coding Reviewed: No changes
- 11/15/2019– Annual Review: No changes. Coding reviewed: No changes
- 05/17/2019– Annual Review: Initial review of Perjeta (pertuzumab). Wording and formatting changes. Simplify diagnostic criteria. Coding Reviewed. No changes.

References

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6. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
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8. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 18, 2025.
    a. Biliary Tract Cancers. V6.2024. Revised January 10, 2024.
    b. Breast Cancer. V6.2024. Revised November 11, 2024.
    c. Central Nervous System Cancers. V3.2024. Revised September 30, 2024.
    d. Colon Cancer V6.2024. Revised January 17, 2025.
    e. Head and Neck Cancers. V2.2025. Revised January 17, 2025.
    f. Rectal Cancer. V5. 2024. Revised January 17, 2025.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.