Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Ado-trastuzumab (Kadcyla®)	MP-RX-FP-48-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of Ado-trastuzumab (Kadcyla®) approved by the Food and Drug Administration (FDA) for the treatment of certain patients with HER2-positive, metastatic breast cancer, and for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

Background Information

Kadcyla, an antibody-drug conjugate (ADC) that utilizes the HER2- targeting properties of trastuzumab to selectively deliver chemotherapy to HER2-overexpressing tumor cells. This targeted approach minimizes toxicity by limiting exposure of DM1 (N-methyl-N-[3-mercapto-1-oxopropyl]-L-alanine ester of maytansinol) to normal cells.

Breast cancer is a type of tumor comprised of malignant (cancerous) cells that start to grow in the breast and may spread (metastasize) to surrounding tissues and other areas of the body (American Cancer Society, 2016). Breast cancer is commonly treated by various modalities which include combinations of surgery, radiation therapy, chemotherapy and hormone therapy (National Cancer Institute, 2019). The prognosis and selection of therapies can be affected by clinical and pathologic features of the tumor. One of these includes the human epidermal growth factor receptor 2 gene ERBB2 which is commonly referred to as HER2. Other names for this gene include NEU, Her-2, HER-2/neu and c-erb B2. Initially the HER2 gene was detected in frozen breast tumor samples. Amplification of the HER2 gene was later correlated to overexpression of protein levels in samples of breast cancer.

The FDA approved indication for Kadcyla includes use as a single agent to treat those with HER2-positive, metastatic breast cancer who previously received trastuzumab and/or taxane therapy or had disease recurrence within 6 months of completing adjuvant therapy.

The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Kadcyla as a preferred option for treatment of individuals with HER2-positive metastatic breast cancer that progresses on first-line trastuzumab-containing regimen. The guidelines do not recommend the use of Kadcyla in the neoadjuvant setting. The updated NCCN guideline provides a category 1 recommendation for use of Kadcyla as a preferred regimen as preferred adjuvant systemic therapy in individuals with HER2+ tumors and locally advanced disease following completion of planned chemotherapy and following mastectomy or lumpectomy. NCCN also provides a level category 2A rating for Kadcyla's use as single-agent therapy for recurrent or metastatic HER2-positive disease that is HR-negative or HR-positive.

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NCCN also provides a 2A recommendation for the use in limited or extensive brain metastases in those with HER2 positive breast cancer.

In the NCCN clinical practice guideline for Head and Neck cancers the NCCN Panel recommends the use of Kadcyla at a category level 2A rating (previously level 2B rating) in certain circumstances as a single-agent systemic therapy for HER2-positive-recurrent disease with distant metastases or unresectable locoregional recurrence or second primary with prior radiation therapy. At this time the guideline's discussion section updates are under progress and there are no published trials discussing the recommendation. There is one clinical study in progress under clinicaltrials.gov.

Definitions and Measures

- HER2 testing (adapted from American Society of Clinical Oncology/College of American Pathologists):
    - 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.

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- 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.
- 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.
- One line of therapy: Single line of 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.

Approved Indications

FDA Approved Indication
Early Breast Cancer Indicated as a single agent for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab -based treatment.
Metastatic Breast Cancer Indicated as a single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • Received prior therapy for metastatic disease, or • Developed disease recurrence during or within six months of completing adjuvant therapy.

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Other Uses

In the NCCN clinical practice guideline for non-small cell lung cancer the NCCN Panel recommends use of Kadcyla (category 2A) in treatment of individuals with HER2 mutations in lung cancer based on a small phase 2 basket trial (Li, 2018). The trial assessed ado- trastuzumab emtansine in patients with metastatic NSCLC and ERBB2 (HER2) mutations. The partial response rate was 44% (95% CI, 22%–69%). The median PFS was 5 months (95% CI, 3–9). Minor toxicities (grade 1–2) included infusion reactions, thrombocytopenia, and transaminitis; no treatment-related deaths were reported. Patients (n = 18) were mostly women (72%), did not smoke cigarettes, and all had adenocarcinoma histology. Another study (Iwama 2022) assessed ado-trastuzumab emtansine in 22 patients with metastatic NSCLC and ERBB2 (HER2) exon 20 mutations.920 The overall response rate with ado-trastuzumab emtansine was 38% (95% CI, 23%–56%). The median overall survival was 8.1 months.

NCCN also provides a 2A recommendation for use in salivary gland tumors. The evidence comes from two basket trials for a total of 13 individuals. At this time, there is a lack of published data from large, randomized trials for both efficacy and safety for this off-label use. Under clinical judgement, the Hematology/Oncology Subcommittee added the use in Salivary Gland tumors.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9354	Injection, ado-trastuzumab emtansine, 1 mg [Kadcyla]

ICD-10	Description
C50.011-C50.929	Malignant neoplasm of breast
C79.81	Secondary malignant neoplasm of breast
D05.00-D05.92	Carcinoma in situ of breast
D04.5	Carcinoma in situ of skin of breast
Z51.11	Encounter for antineoplastic chemotherapy
Z85.3	Personal history of malignant neoplasm of breast

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Medical Necessity Guidelines

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.

Ado-trastuzumab (Kadcyla®)

A. **Criteria For Initial Approval** (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of HER2-positive (HER2+) breast cancer (NCCN 1) confirmed by *one* of the following:

A. Immunohistochemistry (IHC) is 3 +;

OR

B. In situ hybridization (ISH) positive;

AND

C. Used in one of the following ways:

1. Individual has early breast cancer; **AND**
    a. Individual is using as a single agent; **AND**
    b. Individual is using as adjuvant treatment of early non-metastatic breast cancer for residual invasive disease in the breast or axilla after surgery after receiving at least 6 cycles (16 weeks) of neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab (or trastuzumab biosimilars);

OR

2. Individual has metastatic breast cancer disease (DP B IIa); **AND**
    a. Individual is using as a single agent; **AND**
    b. Individual has previously received trastuzumab (or its biosimilar) and a taxane, separately or in combination; **AND**
    c. Individual has either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy;

OR

3. Individual has recurrent unresectable or metastatic breast cancer (NCCN 2A); **AND**
    a. Individual is using in one of the following ways:
        i. Individual is using as third-line therapy and beyond; **OR**
        ii. Individual is using as second-line if not a candidate for fam-trastuzumab deruxtecan; **AND**
    b. Individual is one of the following:
        i. Individual is hormone receptor-negative; **OR**

ii. Individual is hormone receptor-positive with or without endocrine therapy;

OR

ii. Individual has a diagnosis of limited or extensive brain metastases with HER2-positive breast cancer; **AND**
   A. Individual is using as a single agent; **AND**
   B. Using as initial or primary treatment in asymptomatic disease; **OR**
   C. As treatment for recurrent/relapsed disease with stable systemic disease or reasonable systemic treatment options;

OR

iii. Individual has a diagnosis of ERBB2 (HER2) mutation positive recurrent, advanced, or metastatic non-small cell lung cancer (NSCLC) (NCCN 2A, DP B IIa); **AND**
   A. Individual is using as a single-agent; **AND**
   B. Individual is using as subsequent therapy;

OR

iv. Individual has a diagnosis of recurrent HER2+ salivary gland tumors (NCCN 2A); **AND**
   A. Individual has had prior anti-HER2+ therapy (e.g. trastuzumab or trastuzumab biosimilars) (Clinical judgement); **AND**
   B. Using as single-agent systemic therapy.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Kadcyla (ado-trastuzumab) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:
   A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
   B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results (every six months).

ii. For early breast cancer: Kadcyla may be approved for a total of 14 cycles (42 weeks) unless there is disease recurrence or unmanageable toxicity.

iii. For metastatic breast cancer: Until disease progression or unmanageable toxicity.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months

ii. Reauthorization Approval Duration: Up to 6 months

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

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i. When Kadcyla is used in combination with other targeted biologic agents or chemotherapy agents; **OR**

ii. When the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

FDA Approved Indication	Recommended Dose
Early Breast Cancer	3.6 mg/kg given as an intravenous infusion every 3 weeks (21- day cycle).
Metastatic Breast Cancer	3.6 mg/kg given as an intravenous infusion every 3 weeks (21- day cycle).
Exceptions	
None	

Reference Information

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 18, 2022.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
5. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers. Results from a phase II basket trial. J.Clin Oncol 2018:36:2532-2537.
6. NCCN Clinical Practice Guidelines in Oncology™. © 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 18, 2022.
    a. Breast Cancer. V2.2022. Revised December 20, 2021.
    b. Central Nervous System Cancer. V2.2021. Revised September 8, 2021.
    c. Head and Neck Cancers. V1.2022. Revised December 8, 2021.
    d. Non-Small Cell Lung Cancer. V1.2022. Revised December 7, 2021.

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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.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Add NCCN category 2A recommendation for use in HER2-positive recurrent unresectable or metastatic breast cancer when using as third-line therapy or beyond. Update existing criteria for use as a single agentin brain metastases with HER2-positive breast cancer. Add NCCN category 2A recommendation for use in ERBB2(HER2) mutation positive recurrent, advanced, or metastatic NSCLC as a single agent for subsequent therapy. Coding Reviewed: No changes.	11/18/2024	12/17/2024
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

Revised: 10/16/2024