

# Medical Drug Clinical Criteria

<b>Subject:</b>	Kadcyla (ado-trastuzumab)		
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## Overview

This document addresses the use of Kadcyla (ado-trastuzumab). 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.

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.

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. Under clinical judgement, the Hematology/Oncology Subcommittee added the use in Salivary Gland tumors.

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.

## 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  $\geq 6.0$  signals/cell\*
  - Dual-probe HER2/CEP 17 ratio  $\geq 2.0^*$  with an average HER2 copy number  $\geq 4.0$  signals/cell.
  - Dual-probe HER2/CEP17 ratio  $\geq 2.0^*$  with an average HER2 copy number  $< 4.0$  signals/cell.
  - Dual-probe HER2/CEP17 ratio  $< 2.0^*$  with an average HER2 copy number  $\geq 6.0$  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  $\leq 10\%$  of the invasive tumor cells.
- ISH equivocal based on:
  - Single-probe average HER2 copy number  $\geq 4.0$  and  $< 6.0$  signals/cell.
  - Dual-probe HER2/CEP17 ratio  $< 2.0$  with an average HER2 copy number  $\geq 4.0$  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  $\leq 10\%$  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.

## 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.

### Kadcyla (ado-trastuzumab)

Requests for Kadcyla (ado-trastuzumab) may be approved if the following criteria are met:

- 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 its 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 biosimilars) 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.

Requests for Kadcyła (ado-trastuzumab) may not be approved for the following:

- I. When Kadcyła is used in combination with other targeted biologic agents or chemotherapy agents; **OR**
- II. 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

J9354 Injection, ado-trastuzumab emtansine, 1 mg [Kadcyła]

### 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 glands  
C33 Malignant neoplasm of trachea  
C34.00-C34.92 Malignant neoplasm of bronchus and lung  
C50.011-C50.929 Malignant neoplasm of breast  
C79.31 Secondary malignant neoplasm of brain  
C79.81 Secondary malignant neoplasm of breast  
Z51.11 Encounter for antineoplastic chemotherapy

## Document History

Revised: 02/21/2025

Document History:

- 02/21/2025 – Annual Review: No Changes. Wording and formatting updates. Coding Reviewed: Added ICD-10-CM C06.9, C07, C08.0-C08.9, C33, C34.00-C34.92, C79.31. Removed ICD-10-CM D05.00-D05.92 and D04.5.
- 02/23/2024 – 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 agent in 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.
- 02/24/2023 – Annual Review: Add clarifying criteria for use in brain metastases with HER2-positive breast cancer. Ensure trastuzumab biosimilars are also considered within criteria for use in HER2+ salivary gland tumors. Coding Reviewed: No changes.
- 02/25/2022 – Annual Review: Add NCCN 2A recommendation for use in salivary gland tumors. Add NCCN 2A recommendation for use in brain metastases in those with HER2-positive breast cancer. Wording and formatting updates. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: Update existing criteria with clarification for use in early breast cancer and metastatic breast cancer. Coding Reviewed: Added ICD-10-CM D05.00-D05.92, D04.5.
- 02/21/2020 – Annual Review: Update Kadcylla 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 Kadcylla (ado-trastuzumab emtansine). Simplify diagnostic criteria. Minor wording and formatting updates. Coding Review: No changes.

## References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Updated periodically.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Iwama E, Zenke Y, Sugawara S, et al. Trastuzumab emtansine for patients with non-small cell lung cancer positive for human epidermal growth factor receptor 2 exon-20 insertion mutations. *Eur J Cancer* 2022;162:99-106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34959152>.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; 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™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on January 17, 2025..
  - a. Breast Cancer. V6.2024. Revised November 11, 2024.
  - b. Central Nervous System Cancers V3.2024. Revised September 30, 2024.
  - c. Head and neck cancers. V1.2025. Revised November 26, 2024
  - d. Non-Small Cell Lung Cancer. V3.2025. Revised January 14, 2025.

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