Corporate Medical Policy

Ado-Trastuzumab Emtansine (Trastuzumab-DM1) for Treatment of HER-2 Positive Malignancies

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Description of Procedure or Service

Ado-trastuzumab emtansine (Kadcyla™), also known as trastuzumab-DM1 or T-DM1, is an antibody-drug conjugate that links the human epidermal growth factor receptor 2 (HER2) antagonist activity of trastuzumab to the cytotoxic activity of emtansine (DM1). It is an antagonist of HER2 that is intended as treatment for patients with breast cancers that overexpress *HER2*, and it may also have applications for other *HER2*-positive malignancies.

Background
Breast cancer accounts for nearly 1 in 3 cancer diagnoses in women in the U.S. Breast cancer is the most common cancer in women after nonmelanoma skin cancer and ranks second for cancer mortality after lung cancer. Current estimates by the National Cancer Institute project that 266,100 new cases of breast cancer will be diagnosed in women, and approximately 40,900 women will die from 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.

Approximately 20-25% of breast cancers overexpress HER2, a transmembrane glycoprotein receptor with tyrosine kinase activity. HER2, previously called HER2/neu, or ErbB-2, is part of the HER tyrosine kinase receptor family that includes 4 transmembrane receptors: HER1 (also known as epidermal growth factor receptor [EGFR]), HER2, HER3, HER4. These receptors mediate tumor cell growth, survival, and differentiation. 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, and 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) that constitutively activate tyrosine kinase signaling.

HER2 overexpression is associated with reduced time to disease recurrence and poorer prognosis. Before the advent of HER2-targeted therapy, HER2 overexpression was associated with shorter disease free and overall survival than either lymph node–negative or lymph node–positive breast cancers; with lack of responsiveness to tamoxifen therapy; and with altered responsiveness to cytotoxic chemotherapy.

Before FDA approval of ado-trastuzumab emtansine, 3 anti-*HER2* therapies were FDA-approved for *HER2*-positive cancers. These agents arrest tumor cell growth and promote apoptosis by blocking HER2-mediated intracellular signaling pathways that mediate cell growth, differentiation, and survival:

- Trastuzumab (Herceptin®) is an intravenous monoclonal antibody to an extracellular domain of the HER2 receptor (Subdomain IV) that prevents activation of intracellular tyrosine kinase signaling cascades and also promotes antibody-dependent cell mediated cytotoxicity (ADCC).
- Lapatinib (Tykerb®) is an oral tyrosine kinase inhibitor that blocks the intracellular tyrosine kinase domain of HER2 and downstream cell-signaling cascades.
- Pertuzumab (Perjeta™) is a monoclonal antibody to the extracellular dimerization domain of the HER2 receptor (Subdomain II) that, like trastuzumab, prevents activation of intracellular tyrosine kinase signaling cascades and also promotes ADCC.

Trastuzumab is recommended for first-line treatment of patients with *HER2*-positive metastatic breast cancer, either in combination with pertuzumab and a taxane (preferred), or in combination with a taxane (paclitaxel with or without carboplatin, or docetaxel), vinorelbine, or capecitabine. Monotherapy is also an option for first-line treatment. Treatment with trastuzumab plus an anthracycline (doxorubicin or daunorubicin) is not recommended because of unacceptably high rates of cardiac toxicity. Most patients who initially respond to trastuzumab will eventually progress. For second-line treatment of *HER2*-positive metastatic breast cancer that progresses after trastuzumab therapy (either in the adjuvant setting or as first-line treatment for metastatic disease), continuation of HER2 blockade is recommended. For patients not previously exposed to pertuzumab, combination therapy with trastuzumab plus pertuzumab with or without cytotoxic chemotherapy (eg, a taxane or vinorelbine) is recommended. Other treatment options are trastuzumab plus lapatinib, or capecitabine and lapatinib plus capecitabine. In patients who obtain sustained disease control, the optimal duration of *HER2*-targeted therapy is unknown.

Ado-trastuzumab emtansine is an antibody-drug conjugate comprised of trastuzumab and emtansine. Emtansine (previously called DM1 for derivative of maytansine 1) is a sulfur-containing derivative of the potent microtubule inhibitor, maytansine. Emtansine is conjugated to trastuzumab by lysine side chains, forming a stable thioether linker. Ado-trastuzumab emtansine binds HER2 with an affinity comparable with that of trastuzumab. Once internalized, proteolytic degradation of the linker releases both trastuzumab and the active metabolite, maleimidomethyl cyclohexane-1-carboxylate (MCC)-emtansine. MCC-emtansine contains both positive and negative charges and therefore does not readily cross plasma membranes, maintaining intracellular concentrations. Ado-trastuzumab emtansine has been shown to preserve the antitumor activity of trastuzumab. Death of *HER2*-expressing cells therefore results from effects of both active moieties of ado-trastuzumab emtansine.

Comparable pharmacokinetic data suggest that toxicity associated with trastuzumab exposure is the same whether trastuzumab is administered as ado-trastuzumab emtansine or as trastuzumab. Both drugs carry black box warnings for cardiac toxicity and embryo-fetal toxicity.

Regulatory Status

Ado-Trastuzumab Emtansine (Trastuzumab-DM1) for Treatment of HER-2 Positive Malignancies

In February 2013, Kadcyla (ado-trastuzumab emtansine; Genentech) was approved by the FDA through the priority review program 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 6 months of completing adjuvant therapy.

In May 2019, the FDA expanded the indication to include adjuvant treatment of patients with *HER2*-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

Kadcyla™ is not approved by the FDA for the treatment of patients with:

- *HER2*-positive previously untreated metastatic breast cancer, or
- *HER2*-positive locally advanced or metastatic gastric or gastroesophageal junction cancer.

******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 ado-trastuzumab emtansine (trastuzumab-DM1) for treatment of HER2-positive 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 Ado-Trastuzumab Emtansine for Treatment of HER2-Positive Malignancies is covered

The use of ado-trastuzumab emtansine may be considered medically necessary when the following conditions have been met:

1. The patient has human epidermal growth factor receptor 2 (*HER2*)-positive, metastatic breast cancer and has received prior treatment with trastuzumab and a taxane, separately or in combination; and
    a. The patient has received prior treatment for metastatic disease, or
    b. The patient has developed disease recurrence during or within 6 months of completing adjuvant therapy; **OR**
2. The patient has HER2-positive early breast cancer and has residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

When Ado-Trastuzumab Emtansine for Treatment of HER2-Positive Malignancies is not covered

The use of ado-trastuzumab emtansine is considered **investigational** in all other situations, including but not limited to previously untreated progressive or recurrent locally advanced breast cancer, earlier stages of breast cancer, combination treatment with different agents, and treatment of gastric cancer.

Policy Guidelines

For individuals who have *HER2*-positive progressive/recurrent or metastatic breast cancer who failed second-line treatment, including trastuzumab and a taxane, who receive ado-trastuzumab emtansine, the evidence includes 2 randomized controlled trials (RCTs), 3 uncontrolled trials and 2 meta-analysis. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Based on results of the pivotal EMILIA trial, ado-trastuzumab emtansine was approved by the U.S. Food and Drug Administration for patients with *HER2*-positive metastatic breast cancer who have been previously treated with trastuzumab and a taxane. The EMILIA trial reported an improvement in progression-free survival of 3.2 months and an absolute improvement in overall survival of 5.8 months for patients treated with ado-trastuzumab emtansine compared with lapatinib plus capecitabine. Uncontrolled studies corroborate the efficacy of ado-trastuzumab emtansine with objective response rates reported as ranging from 26% to 41 % of patients in 3 phase 2 studies. Adverse events from ado-trastuzumab emtansine treatment are common. 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 previously untreated progressive/recurrent locally advanced breast cancer or metastatic breast cancer who receive ado-trastuzumab emtansine, the evidence includes a RCT and an uncontrolled trial. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. While the phase 2 trial reported longer PFS with ado-trastuzumab emtansine than with trastuzumab plus docetaxel, the trial was an open-label and progression assessed by investigators. Results of the subsequent phase 3 MARIANNE trial failed to show any PFS advantage of trastuzumab emtansine with or without pertuzumab compared to trastuzumab plus taxane. Secondary analysis of this trial provided better patient-reported outcomes such as quality of life, taxane-related symptoms, and rates of nausea, diarrhea, and alopecia in patients receiving trastuzumab emtansine compared to trastuzumab plus taxane. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who have *HER2*-positive previously untreated early-stage breast cancer who receive neoadjuvant T-DM1, the evidence includes a phase 3 RCT. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. In the phase 3 KRISTINE trial, patients treated with T-DM1 plus pertuzumab had an 11% lower pathologic response than patients treated with docetaxel, carboplatin, and trastuzumab plus pertuzumab. Grade 3 and 4 adverse events were lower than with the control treatment, and also lower than expected from other studies on T-DM1. Therefore, corroboration of the results of the KRISTINE trial are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have HER2-positive early-stage breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment who receive adjuvant T-DM1, the evidence includes a phase 3 RCT. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The phase 3 KATHERINE trial randomly assigned patients to postoperative T-DM1 or trastuzumab for the succeeding 42 weeks. A significant reduction of nearly one-half in the risk of iDFS (invasive breast cancer or death), including the risk of distant recurrence, was observed. Overall, there was an absolute improvement of 11.3 percentage points in the rate of iDFS. The trial was underpowered to detect a significant reduction in mortality and survival benefit was not observed. The hazard ratio for death was 0.70 (95% CI: 0.47 to 1.05). More serious adverse events occurred in patients who received T-DM1 than in those who received trastuzumab (12.7% vs 8.1%), and more patients discontinued T-DM1 than trastuzumab (18.0% vs 2.1%) before the completion of the anticipated 14 postsurgical cycles. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who have *HER2*-positive locally advanced or metastatic gastric or gastroesophageal junction cancer who receive ado-trastuzumab emtansine, the evidence includes a RCT. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Results have shown no survival advantage of trastuzumab emtansine over physician's choice of weekly paclitaxel or docetaxel every 3 weeks. Grade 3 and 4 adverse events were numerically lower in the T-

DM1 group (59.8% vs 70.3%), while rates of serious adverse events, fatal adverse events, and treatment discontinuation due to adverse events were similar. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

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: *J9354, 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]. 5.01.22, 3/14/2013

Senior Medical Director – 5/2013

Specialty Matched Consultant Advisory Panel – 8/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.22, 3/13/2014

Specialty Matched Consultant Advisory Panel- 8/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.22, 3/12/2015

Specialty Matched Consultant Advisory Panel- 8/2015

Senior Medical Director review- 8/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.22, 10/15/2015

Medical Director review 8/2016

Specialty Matched Consultant Advisory Panel 8/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.22, 10/13/2016

Medical Director review 10/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.22, 7/13/2017

Specialty Matched Consultant Advisory Panel 8/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.22, 7/12/2018

Specialty Matched Consultant Advisory Panel 8/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.22, 7/11/2019

Genentech, Inc. Kadcyla (ado-trastuzumab emtansine) for injection, for intravenous use. Highlights of prescribing information. May 2019. Available at: https://www.gene.com/download/pdf/kadcyla_prescribing.pdf. Last accessed July 2019.

Specialty Matched Consultant Advisory Panel 8/2019

Medical Director review 8/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.22, 7/16/2020

Specialty Matched Consultant Advisory Panel 8/2020

Policy Implementation/Update Information

6/11/13 New Evidence Based Guideline developed. "The use of ado-trastuzumab emtansine may be appropriate when all of the following conditions have been met: •Patient has HER2-positive, metastatic breast cancer. •Patient has received prior treatment for metastatic disease, or has developed recurrent disease within 6 months of completing adjuvant therapy. •Patient has received prior treatment with trastuzumab and a taxane." "The use of ado-trastuzumab emtansine is not recommended in all other situations, including but not limited to earlier stages of breast cancer, combination treatment with different agents, and treatment of gastric cancer." Senior Medical Director review 5/18/2013. (btw)

7/16/13 Added new HCPCS code, C9131, to Billing/Coding section. (btw)

9/10/13 Specialty Matched Consultant Advisory Panel review 8/21/13. No change to guideline. (btw)

12/31/13 Added 2014 HCPCS code, J9354 to Billing/Coding section. Deleted HCPCS code C9131. (btw)

4/29/14 Reference added. (btw)

9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No change to guideline. (lpr)

10/1/15 Evidence Based Guideline converted to Corporate Medical Policy. Senior Medical Director review. Reference added. Specialty Matched Consultant Advisory Panel review 8/26/2015. Under Description section: deleted the word "oral" from the third bullet "Pertuzumab (Perjeta™) is a monoclonal antibody." No change to policy statement. Notification given 10/1/15 for effective date 12/30/15. (lpr)

2/29/16 Updated Policy Guidelines section. Reference added. No change to policy statement. (lpr)

12/30/16 Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. Updated Description and Policy Guidelines sections. Added HCPCS codes S0353, S0354 to Billing/Coding section. Reference added. Medical director review 10/2016. Notification given 12/30/16 for effective date 4/1/17. (lpr)

9/15/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. Reference added. No change to policy statement. (lpr)

10/26/18 Added additional clinical trial information within Policy Guidelines section relevant to HER2-positive previously untreated early-stage breast cancer. Specialty Matched

Consultant Advisory Panel review 8/22/2018. References added. No change to policy statement. (krc)

10/1/19 Added the following indication to "When Covered" section: "the patient has HER2-positive early breast cancer and has residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment," and added related clinical evidence to Policy Guidelines. Restructured Policy Statements for clarity. Minor edits and updates made throughout Description and Policy Guidelines sections for clarity. References added. Medical Director review 8/2019. Specialty Matched Consultant Advisory Panel review 8/21/2019. (krc)

11/24/20 Minor typographical errors made for clarity. Reference added. Specialty Matched Consultant Advisory Panel review 8/2020. No change to policy intent. (krc)