Effective November 1, 2018, refer to Palmetto Article A56141

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Kadcyla® (ado-trastuzumab emtansine)

Policy #:	658	Effective Date:	September 1, 2015
Category:	Pharmacology	Latest Review Date:	July 2017

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Kadcyla® (ado-trastuzumab emtansine), 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). The HER2 antagonist is intended as treatment for patients with breast cancers that overexpress HER2, and it may also have applications for other HER-2 positive malignancies.

Metastatic breast cancer accounts for nearly 1 in 3 cancer diagnoses in U.S. women. Breast cancer is the most common cancer in women after nonmelanoma skin cancer and ranks second for cancer mortality after lung cancer. In 2017, an estimated 252,710 new cases of breast cancer will be diagnosed in women, and approximately 40,610 women will die from breast cancer.

Metastatic breast cancer has a poor prognosis. In a cohort of 3524 women diagnosed with breast cancer between 1992 and 2007, median (overall survial was 39.2 months among patients with de novo stage IV breast cancer 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 or older, visceral disease, shorter disease-free interval, negative hormone receptor status, and HER2-positive status.

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

Human Epidermal Growth Factor Receptor 2

Approximately 20-25% of breast cancers overexpress human epidermal growth factor receptor 2 (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 four transmembrane receptors (HER1 [also known as epidermal growth factor receptor 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, 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 initiate 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.

Treatment of HER2-Positive Breast Cancer
Before FDA approval of ado-trastuzumab emtansine, three 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 an intravenous 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 antibody-dependent cell-mediated cytotoxicity.

Trastuzumab is recommended for first-line treatment of patients with HER2-positive metastatic breast cancer, either in combination with pertuzumab and a taxane (preferred); in combination with a taxane (paclitaxel with or without carboplatin, or docetaxel), vinorelbine, or capecitabine; or as monotherapy. 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 (e.g., 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.

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.

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Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service prior to November 1, 2018:

Blue Advantage will treat Kadcyla® (ado-trastuzumab emtansine) as a **covered benefit as a single agent therapy for individuals with metastatic breast cancer who meet ALL** of the criteria below:

- Individuals have previously received trastuzumab and taxane, separately or in combination**; and**
- Individuals has **ONE** of the following:
    1. Received prior therapy for metastatic disease; **or**
    2. Developed disease recurrence during or within six months of completing adjuvant therapy; **and**
- Breast tumor(s) are HER2 positive as documented by one of the following:
    1. Immunohistochemistry (IHC) is 3+; **or**
    2. In situ hybridization (ISH) positive by any of the following:
        a. Single probe average HER2 copy number greater than or equal to 6.0 signals/cell; **or**
        b. Dual-probe HER2/CEP17 ratio greater than or equal to 2.0; **or**
        c. Dual-probe HER2/CEP17 ratio less than 2.0 with an average HER2 copy number greater than or equal to 6.0 signals/cell; **and**
- Only used in a single line of therapy.

Blue Advantage will treat Kadycyla® (ado-trastuzumab emtansine) as a **non-covered benefit** and as **investigational** in all other situations, including but not limited to earlier stages of breast cancer, combination treatment with different agents, and treatment of gastric cancer.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

HER2-Positive, Previously Treated Metastatic Breast Cancer

EMILIA (N=991) was a phase 3, randomized, stratified, active-controlled, open-label trial conducted in 26 countries (27% of patients from the United States). Patients had unresectable, locally advanced, or metastatic human epidermal growth factor receptor 2 (*HER2*)–positive breast cancer previously treated with trastuzumab and a taxane. Median age was 53 years, approximately 37% of patients had 3 or more metastatic sites, and 68% had visceral disease

involvement. Patients were randomized to intravenous infusions of ado-trastuzumab emtansine 3.6 mg/kg every 21 days or to self-administered oral lapatinib 1250 mg daily plus oral capecitabine 1000 mg/m^2 every 12 hours for the first 14 days of each 21-day treatment cycle. Primary efficacy outcomes were progression-free survival (PFS) determined by an independent review committee, and overall survival (OS). PFS was 9.6 months in the ado-trastuzumab emtansine (T-DM1) group and 6.4 months in the lapatinib plus capecitabine group (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.55 to 0.77). At a median follow-up of 19 months, an interim analysis of OS crossed the predetermined stopping boundary, and the trial was discontinued. OS was 30.9 months in the T-DM1group and 25.1 months in the lapatinib plus capecitabine group (HR=0.68; 95% CI, 0.55 to 0.85) (see Table 1).

T-DM1has a black box for hepatotoxicity, cardiotoxicity, and embryo-fetal toxicity. In the event of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity, or peripheral neuropathy with T-DM1, temporary treatment interruption, dose reduction, or discontinuation may be required.

Table 1. EMILIA: Results

	Ado-trastuzumab Emtansine (n=495)	**Lapatinib Plus Capecitabine (n=496)**	**Hazard Ratio (95% CI)**	**p[a]**
IRC-assessed median PFS, mo[b]	9.6	6.4	0.65 (0.55 to 0.77)	<0.001
Stratified by world region				
Western Europe (n=317)	–	–	0.56 (0.41 to 0.74)	–
United States (n=270)	–	–	0.70 (0.51 to 0.98)	–
Asia (n=158)	–	–	0.74 (0.50 to 1.08)	–
Other (n=246)	–	–	0.73 (0.51 to 1.03)	–
Stratified by number of prior chemotherapy regimens for advanced disease				
0-1 (n=609)	–	–	0.68 (0.55 to 0.85)	–
≥1 (n=382)	–	–	0.63 (0.49 to 0.82)	–
Stratified by visceral involvement				
Yes (n=669)	–	–	0.55 (0.45 to 0.67)	–
No (n=322)	–	–	0.96 (0.71 to 1.30)	–
Investigator-assessed median PFS, mo	9.4	5.8	0.6 (0.56 to 0.77)	<0.001
Sensitivity analysis median PFS,[c] mo	9.5	6.7	0.68 (0.57 to 0.81)	<0.001
Overall survival[b]				
Median follow-up ≈13 mo				
Median OS, mo	–	–	0.62 (0.48 to 0.81)	<0.001[d]
Estimated 1-year OS (95% CI), %	85.2 (82.0 to 88.5)	78.4 (74.6 to 82.3)	–	–
Median follow-up ≈19 mo[e]				
Median OS, months	30.9	25.1	0.68 (0.55 to 0.85)	<0.001[f]
Estimated 2-year OS (95% CI), %	64.7 (59.3 to 70.2)	51.8 (45.9 to 57.7)	–	–
Median months to symptom progression[g]	7.1	4.6	0.80 (0.67 to 0.95)	0.012
	T-DM1 (n=397)[h]	**Lapatinib Plus Capecitabine (n=389)[h]**	**Difference (95% CI)**	**p[i]**

IRC-assessed ORR (95% CI), %[j]	43.6 (38.6 to 48.6)	30.8 (26.3 to 35.7)	12.7 (6.0 to 19.4)	<0.001
Partial response, %	42.6	30.3	–	–
Complete response, %	1.0	0.5	–	–
Median duration of OR (95% CI), mo	12.6 (8.4 to 20.8)	6.5 (5.5 to 7.2)	–	–

CI: confidence interval; IRC: independent review committee; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.
[a] Stratified log-rank test.
[b] Primary efficacy end point.
[c] Data for patients who received nonprotocol breast-cancer treatment before documented progression was censored at the last tumor assessment before initiation of the nonprotocol treatment. Nonprotocol treatments comprised (1) any therapies intended for the treatment of breast cancer, including cytotoxic chemotherapy (other than that specified by the trial protocol), immunotherapy, hormonal therapy, and biologic agents; and (2) radiotherapy other than palliative radiotherapy to treat painful bone metastases.
[d] Did not cross the O'Brien-Fleming stopping boundary of p<0.001.
[e] Median follow-up in the ado-trastuzumab emtansine group was 19.1 months (range, 0-40) and in the lapatinib plus capecitabine group, 18.6 months (range, 0-41).
[f] Crossed the O'Brien-Fleming stopping boundary of p<0.004.
[g] Defined as the time from randomization to the first decrease of at least 5 points from baseline Functional Assessment of Cancer Therapy–Breast, Trial Outcome Index (FACT-B TOI) in women with at least 1 postbaseline score (n not reported).
[h]80% of patients in the ado-trastuzumab emtansine group and 78% of patients in the lapatinib plus capecitabine group had measurable disease at baseline.
[i] Stratified Mantel-Haenszel chi-square test.
[j] Defined as the combined incidence of complete response and partial response.

Two exploratory analyses of the EMILIA trial have been published subsequently. Krop et al (2015) examined outcomes in patients with central nervous system (CNS) metastases. Patients with untreated and/or symptomatic CNS metastases or with CNS-only disease were excluded from the EMILIA trial. For the post-hoc analyses, patients with treated, asymptomatic CNS metastases at baseline (n=45 in the ado-trastuzumab emtansine group; n=50 in the control group) were reviewed. At median follow-up of 19 months, median PFS was similar between treatment groups (5.9 months ado-trastuzumab emtansine vs 5.7 months controls; HR, 1.00 [95% CI, 0.54 to 1.84]; stratified [by world region, prior chemotherapy regimen for advanced or metastatic disease, and presence of visceral metastases], log-rank test, p=1.00), but median OS was longer in the ado-trastuzumab emtansine group (26.8 months vs 12.9 months; HR, 0.38 [95% CI, 0.18 to 0.80]; stratified log-rank test, p=0.008). No new safety signals were identified. Welslau et al (2014) reported greater improvements in patient-reported outcomes (time to symptom worsening and increase in diarrhea symptoms) with ado-trastuzumab emtansine compared with capecitabine-lapatinib (control). The proportion of patients experiencing a clinically significant improvement in symptoms was similar between groups.

In 2014, Krop et al published results of the TH3RESA trial in patients with progressive disease after two or more HER2-targeted treatment regimens for recurrent or metastatic breast cancer.19 TH3RESA was an international, Phase III, open-label randomized controlled trial (RCT) that compared ado-trastuzumab emtansine with treatment of physician's choice (chemotherapy, hormone therapy, and/or HER2-targeted therapy). Eligible patients had been treated with both trastuzumab and lapatinib in the advanced setting and a taxane in any setting. Patients were randomized 2:1 to trastuzumab emtansine (n=404) or physician's choice treatment (n=198), stratified by world region (U.S. vs Western Europe vs other), number of previous regimens for advanced disease (2-3 vs >3), and presence of visceral disease (any vs none). Coprimary end points were investigator-assessed PFS and OS. Analysis was intention to treat. Most patients

(83%) in the physician's choice group received HER2-targeted therapy plus chemotherapy (most commonly vinorelbine); 80% of patients in this group received trastuzumab. Median treatment duration was 2.7 months in the physician's choice group versus 4.2 months in the ado-trastuzumab emtansine group. At median follow-up of approximately seven months, median PFS was almost twice as long in the ado-trastuzumab group compared with the physicians' choice group (6.2 months vs 3.3 months; stratified HR, 0.53 [95% CI, 0.42 to 0.66]; log-rank test, p<0.001). This finding was replicated in subgroup analyses of patients who did (n=149) or did not (n=49) receive trastuzumab in the physician's choice group, and in several other subgroup analyses. For U.S. patients (n=99 in the ado-trastuzumab group; n=48 in the physician's choice group), median PFS did not differ statistically between groups (HR, 0.71 [95% CI, 0.44 to 1.14]). In interim OS analysis, 15% of patients in the ado-trastuzumab emtansine group versus 22% in the physician's choice group died a statistically nonsignificant result due to statistical correction (O'Brien-Fleming stopping boundary). Incidence of Grade 3 or greater adverse events was lower in the ado-trastuzumab emtansine group compared with the physician's choice group (32% vs 43%, respectively). Of several hematologic adverse events (neutropenia, febrile neutropenia, anemia, leukopenia, thrombocytopenia), only thrombocytopenia occurred more commonly in the ado-trastuzumabemtansine group (15% vs 3%). Nine patients (2%) who received ado-trastuzumab emtansine had Grade 3 or worse hemorrhage compared with one patient (<1%) who received physician's choice treatment.

Two meta-analyses by Ma et al and Shen et al, both published in 2016, have supported findings that treatment with single-agent T-DM1 is superior to capecitabine plus lapatinib or physician choice in patients with metastatic breast cancer previously treated with trastuzumab and a taxane, separately or in combination. In the Ma analysis, instead of pooling OS or PFS data, the reviewers pooled the percentage of patients with an event (death or PFS) at discrete time interval (2, 4, 6, 8, 10, 12 months) for the phase 2 and 3 trials. In the Shen analysis, the risk of bias or quality assessment of studies included in the meta-analysis was not conducted. In the efficacy analysis, the pooled odds (2 trials) for OS was 0.60 (95% CI, 0.48 to 0.75) and the pooled odds for PFS (3 trials) was 0.60 (95% CI, 0.53 to 0.69). For the safety analysis, increased transaminases (OR=4.040; 95% CI 1.429 to 11.427), thrombocytopenia (OR=8.500; 95% CI, 3.964 to 18.226), and fatigue (OR=1.288; 95% CI 1.041 to 1.593) occurred more frequently in patients who received T-DM1 compared with controls.

Uncontrolled Trials

Three single-arm, open-label, phase 2 studies (conducted in the United States) enrolled patients with *HER2*-positive metastatic breast cancer and measurable disease. In the TDM4374g study, 110 patients were enrolled who had been previously treated with trastuzumab, lapatinib, a taxane, an anthracycline, and capecitabine. The median patient age was 53 years old; 98% of the patients were female, 74% of patients had 3 or more metastatic sites, and all patients had received a median of 7 systemic treatments for metastatic disease. The TDM4258g study enrolled 112 patients previously treated with *HER2*-directed therapy (trastuzumab or lapatinib). The median patient age was 55 years old; 75% of the patients had 3 or more metastatic sites, and all patients had received a median of 5 systemic treatments for metastatic disease. Patients in both studies received ado T-DM1 3.6 mg/kg intravenously every 3 weeks with dose modifications for adverse events. Objective response rate (ORR; defined as complete plus partial responses) determined by an independent radiologic facility was the primary efficacy outcome in

both studies. In TDM4374g (more pretreatment), ORR was 35% (95% CI, 26% to 44%). In TDM4258g (less pretreatment), ORR was 26% (95% CI, 18% to 34%). There were no complete responses. The median PFS (a secondary outcome) was 6.9 months (95% CI, 4.2 to 8.4 months) in TDM4374g and 4.6 months (95% CI, 3.9 to 8.6 months) in TDM4258g (see Table 2).

In the third study, 64 patients with *HER2*-positive, locally advanced breast cancer were treated with ado-trastuzumab emtansine 3.6 mg/kg plus pertuzumab (840-mg loading dose, then 420 mg subsequently) once every 3 weeks. The primary efficacy end point was investigator-assessed ORR. Of the 64 patients, 43 were in the second-line or greater setting; 21 were in the first-line setting. Overall, the ORR was 41%, 57% in first-line setting and 33% in the other settings, with a median PFS of 7.7 months (6.6 months in first-line, 5.5 months in the other settings).

Table 2. Phase II Studies: IRF Efficacy Outcomes

Outcomes	**TDM 4374g Krop (2012) (N=110)**		**TDM 4258g Burris (2011)** (N=112)	
	Result	**95% CI**	**Result**	**95% CI**
Objective response, %	34.5	26.1 to 43.9	25.9	18.4 to 34.4
Complete response, %	0	NR	0	NR
Partial response, %	34.5	NR	25.9	NR
Stable disease, %	NR	NR	49.1	NR
Clinical benefit rate,[a] %	48.2	38.8 to 57.9	NR	NR
Median duration of objective response, mo	7.2	4.6 to NE	Not reached	6.2 to NE
Median PFS, mo	6.9	4.2 to 8.4	4.6	3.9 to 8.6

CI: confidence interval; IRF: independent radiologic facility; NE: not estimable; NR: not reported; PFS: progression-free survival.
[a] Clinical benefit rate was defined as objective response (complete or partial) plus stable disease ≥6 months.

Section Summary: HER2-Positive, Previously Treated Metastatic Breast Cancer
Multiple RCTs, prospective single-arm trials, and meta-analyses of these studies in the second-line setting of *HER2*-positive breast cancer have shown improvement in OS with T-DM1 compared with chemotherapy with lapatinib plus capecitabine. The pivotal EMILIA trial reported an improvement of 3.2 months in PFS and an absolute improvement of 5.8 months in OS for patients treated with T-DM1 compared with those who received lapatinib plus capecitabine. The pooled odds from a meta-analysis reported a 40% relative reduction in the hazard of death (HR=0.60; 95% CI, 0.48 to 0.75). Uncontrolled studies have corroborated the efficacy of T-DM1 with ORRs ranging from 26% to 41% of patients in 3 phase 2 studies.

HER-2 Positive, Progressive or Recurrent or Metastatic Breast Cancer
Hurvitz et al (2013) conducted a phase 2, open-label, RCT (TDM4450g) of T-DM1 as first-line treatment of *HER2*-positive metastatic or recurrent locally advanced breast cancer. With a median follow-up of 14 months, median PFS was 14.2 months in the T-DM1 group and 9.2 months in the trastuzumab plus docetaxel group (HR=0.59; 95% CI, 0.36 to 0.97; p=0.04). Respective ORRs were 64% and 58% (p=0.46). Survival results were confounded because 50% of patients in the control group crossed over to T-DM1 after progression. At 23-month median follow-up, preliminary analysis showed no statistical difference between groups (13 deaths in each group; HR=1.06; 95% CI, 0.48 to 2.35; p=0.89). Fewer grade 3 or 4 adverse events (46% vs

91%), adverse events leading to treatment discontinuation (7% vs 41%), and serious adverse events (20% vs 26%) occurred in the T-DM1 group than in the comparator group.

Perez et al (2014) reported the results of the phase 3 MARIANNE trial (NCT01120184) in patients with centrally assessed HER2-positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer with a 6-month or more interval since treatment in the neoadjuvant setting with taxanes or vinca alkaloids. Patients were randomized 1:1:1 to T-DM1 plus pertuzumab (n=363), T-DM1 alone (n=367), or trastuzumab plus taxane (docetaxel or paclitaxel) (n=365). Neither T-DM1 plus pertuzumab nor T-DM1 alone showed PFS superiority over the current standard of care (ie, trastuzumab plus taxane). Median PFS durations were 15.2, 14.1 and 13.7 months, respectively, in the 3 arms. Respective response rates were 64.2%, 59.7%, and 67.9%; median response durations were 21.2, 20.7, and 12.5 months. Compared with trastuzumab plus taxane arm, the hazard ratios for PFS in T-DM1 with and without pertuzumab were 0.87 (95% CI, 0.69 to 1.08) and 0.91 (95% CI, 0.73 to 1.13), respectively. In the first interim OS analysis, median OS was not reached in any treatment group. Secondary analysis of patient-reported outcomes (eg, quality of life) showed that T-DM1 with or without pertuzumab maintained baseline health-related quality of life longer than did trastuzumab plus taxane. The median time for a clinically meaningful decrease in health-related quality of life from baseline was 3.6 months with trastuzumab plus taxane compared to 7.7 months with T-DM1 and 9.0 months with T-DM1 plus pertuzumab. The incidences of grade 3 or 4 adverse events were 54.1%, 45.4% and 46.2% in the trastuzumab plus taxane, T-DM1 alone, and T-DM1 plus pertuzumab arms, respectively.

Section Summary: HER2-Positive, Progressive or Recurrent Metastatic Breast Cancer
The pivotal RCT conducted among *HER2*-positive progressive or recurrent locally advanced breast cancer patients failed to show the superiority of regimens containing T-DM1 over the current standard of care (ie, trastuzumab plus taxane). Median PFS durations were 15.2, 14.1, and 13.7 months with T-DM1 plus pertuzumab, T-DM1 alone, and trastuzumab plus taxane, respectively. Secondary analysis showed that median time for a clinically meaningful decrease in health-related quality of life from baseline with T-DM1 with (9.0 months) or without pertuzumab (7.7 months) was longer than with trastuzumab plus taxane (3.6 months). The incidence of grade 3 or greater adverse events was lower in T-DM1 arms compared with trastuzumab plus taxane.

HER2-Positive, Locally Advance or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma
GATSBY trial (NCT01641939) evaluated the efficacy and tolerability of T-DM1 in the second-line setting of *HER2*-positive advanced gastric cancer. Thuss-Patience et al (2017) reported on the final analysis of the open-label GATSBY trial, which randomized 415 patients with *HER2*-positive unresectable locally advanced or metastatic gastric or gastroesophageal junction cancer to T-DM1 (3.6 mg/kg every 3 weeks or 2.4 mg/kg every week) or physicians' choice of paclitaxel (80 mg/m^2 every week) or docetaxel (75 mg/m2 every 3 weeks). Patients had to have progressed during or after first-line fluoropyrimidine plus platinum therapy with or without *HER2*-targeted therapy. The primary end point (OS) was assessed in the intention-to-treat population. Median OS was 7.9 months (95% CI, 6.7 to 9.5) with T-DM1 2.4 mg/kg weekly and 8.6 months (95% CI, 7.1 to 11.2) with taxane treatment (HR=1.15, 95% CI, 0.87 to 1.51, p=0.86). 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 discontinuations due to adverse events were similar. Thus, T-DM1 did not show an efficacy benefit over taxane for *HER2*-positive local advanced or metastatic gastric or gastroesophageal junction cancer.

Section Summary: HER2-Positive Locally Advanced or Metastatic Gastric or Gastroesophageal Junction

The pivotal RCT conducted among patients with *HER2*-positive locally advanced or metastatic gastric or gastroesophageal junction cancer failed to show the superiority of T-DM1 over physicians' choice of chemotherapy. Median OS durations were 7.9 months and 8.6 months (p=0.86), respectively.

SUMMARY

For individuals who have human epidermal growth factor receptor 2 (*HER2*) positive metastatic breast cancer who failed treatment for metastatic disease, including trastuzumab and a taxane, who receive ado-trastuzumab emtansine, the evidence includes 2 randomized controlled trials (RCTs), 3 uncontrolled trials, and 2 meta-analyses. 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 of 3.2 months in progression-free survival (PFS) and an absolute improvement of 5.8 months in overall survival for patients treated with ado-trastuzumab emtansine compared with those who received lapatinib plus capecitabine. Uncontrolled studies have corroborated 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 that the technology results in a meaningful improvement in the net health outcome.

For individuals who have *HER2*-positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer who receive ado-trastuzumab emtansine, the evidence includes 1 RCT and 1 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 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 locally advanced or metastatic gastric or gastroesophageal junction cancer who receive ado-trastuzumab emtansine, the evidence includes 1 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.

Key Words:

Ado-Trastuzumab Emtansine, Kadcyla, T-DM1, Perjeta, breast cancer, HER2 positive

Approved By Governing Bodies

In February 2013, Kadcyla® (ado-trastuzumab emtansine; Genentech, South San Francisco, CA) was approved by FDA 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.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

HCPCS Codes:

J9354 Injection, ado-trastuzumab emtansine, 1 mg **(effective 01/01/2014)**

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Policy History

Medical Policy Group, September, 2015
Medical Policy Group, August 2016
Medical Policy Group, July 2017
Medical Policy Group, November 2018