

## PHARMACY / MEDICAL POLICY – 5.01.514

## Herceptin® (trastuzumab) and Other HER2 Inhibitors

Effective Date: June 1, 2018

Last Revised: May 3, 2018

Replaces: 5.01.12


RELATED MEDICAL POLICIES:

2.04.76 Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers

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## Introduction

Genes contain instructions for how a cell makes proteins. Proteins drive the functions within a cell. HER2 (human epidermal growth factor receptor 2) is a gene that can affect the development of breast cancer. About one in four or five cases of breast cancer are caused by the HER2 gene making too many copies of itself. And because too many HER2 genes are being made, too much HER2 protein also is being made. HER2 inhibitors are drugs that block the function of the HER2 protein. They essentially cut off the growth signals to the cancerous cells. This policy discusses when HER2 inhibitors may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

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**Note:** Initial approval period for injectable drugs listed below will be 12 months.

**Note:** Initial approval period for oral drugs listed below will be 3 months. Continued approval beyond the first 3 months will require documentation showing objective response to therapy.

## HER2-positive Breast Cancer

| Drug                            | Medical Necessity   |
|---------------------------------|---|
| <b>Oral Drugs</b>               |   |
| <b>Tykerb® (lapatinib)</b>      | <p><b>Tykerb® (lapatinib) may be considered medically necessary for the treatment of HER2-positive breast cancer:</b></p> <ul style="list-style-type: none"> <li>In patients with advanced or metastatic disease who received prior therapy including an anthracycline, a taxane, and trastuzumab and progressed on trastuzumab</li> <li>In postmenopausal patients with hormone receptor-positive, metastatic disease for whom hormonal therapy is indicated, in combination with letrozole</li> </ul> <p><b>This includes use as adjuvant therapy, neoadjuvant therapy, and treatment of metastatic disease. This medication may be medically necessary:</b></p> <ul style="list-style-type: none"> <li>For adjuvant treatment of HER2-positive breast cancer (node positive or negative) as part of several different combination therapy regimens following prior chemotherapy</li> <li>For treatment of HER2-positive metastatic breast cancer in combination therapy</li> </ul> |
| <b>Nerlynx® (neratinib)</b>     | <p><b>Nerlynx® (neratinib) may be considered medically necessary for use as extended adjuvant treatment in adult patients with breast cancer whose tumors overexpress or have amplified HER2 protein (HER2-positive breast cancer). This medication may be medically necessary when all of the following are true:</b></p> <ul style="list-style-type: none"> <li>Neratinib is used as adjuvant therapy</li> <li>Neratinib is used following adjuvant trastuzumab-based therapy</li> <li>Patient has stage III or lower breast cancer</li> <li>Patient has HER2-positive breast cancer</li> </ul> <p><b>*Note:</b> Total duration of neratinib therapy will be limited to maximum of 1 year</p>   |
| <b>Injectable Drugs</b>         |   |
| <b>Herceptin® (trastuzumab)</b> | <p><b>Herceptin® (trastuzumab) may be considered medically necessary for the treatment of patients with HER2-positive breast cancer. This includes use as adjuvant therapy,</b></p>   |



| Drug   | Medical Necessity  |
|--|--|
|  | <p><b>neoadjuvant therapy, and treatment of metastatic disease:</b></p> <ul style="list-style-type: none"> <li>• For adjuvant treatment of HER2-positive breast cancer (node positive or negative) as part of several different combination therapy regimens or as a single agent following prior chemotherapy. Trastuzumab is administered via IV infusion for a total of 52 weeks.</li> <li>• For treatment of HER2-positive metastatic breast cancer in combination therapy or as a single agent. Trastuzumab is administered as a weekly IV infusion until disease progression.</li> </ul>   |
| <p><b>Perjeta® (pertuzumab)</b></p>                | <p><b>Perjeta® (pertuzumab) may be considered medically necessary for the treatment of previously untreated HER2-positive breast cancer or recurrent breast cancer after adjuvant therapy, when used in combination with trastuzumab and docetaxel or paclitaxel. This includes use as adjuvant therapy, neoadjuvant therapy, and treatment of metastatic disease.</b></p> <p><b>Perjeta® (pertuzumab) may be considered medically necessary when used in combination with trastuzumab and chemotherapy as:</b></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.</li> </ul> |
| <p><b>Kadcyla™ (ado-trastuzumab emtansine)</b></p> | <p><b>Kadcyla™ (ado-trastuzumab emtansine) may be considered medically necessary when all of the following conditions have been met:</b></p> <ul style="list-style-type: none"> <li>• Kadcyla is used as a single agent</li> <li>• Patient has HER2-positive, metastatic breast cancer</li> <li>• Patient has received prior treatment for metastatic disease, or has developed recurrent disease within 6 months of completing adjuvant therapy</li> <li>• Patient has received prior treatment with trastuzumab and a taxane, either separately or in combination</li> </ul> <p><b>All other uses of ado-trastuzumab emtansine are considered</b></p>  |



| Drug | Medical Necessity  |
|------|--|
|      | investigational, including but not limited to earlier stages of breast cancer, combination treatment with different agents, and treatment of gastric cancer. |

## Conditions Other Than HER2-positive Breast Cancer

| Drug                            | Medical Necessity   |
|---------------------------------|---|
| <b>Injectable Drugs</b>         |   |
| <b>Herceptin® (trastuzumab)</b> | <p><b>Herceptin® (trastuzumab) may be considered medically necessary when used in combination with cisplatin and capecitabine or 5-fluorouracil, for palliative treatment of patients with metastatic gastric cancer or gastroesophageal junction adenocarcinoma whose tumors overexpress the HER2 protein (HER2-positive).</b></p> <p><b>Note:</b> Trastuzumab is not recommended for use with anthracyclines in palliative therapy for metastatic gastric cancer or gastroesophageal junction adenocarcinoma.</p> |

## Conditions Other Than HER2-positive Breast Cancer

| Drug                            | Investigational   |
|---------------------------------|---|
| <b>Oral Drugs</b>               |   |
| <b>Tykerb® (lapatinib)</b>      | Except as noted above, Tykerb® (lapatinib) is considered investigational for the treatment of conditions other than HER2-positive breast cancer including, but not limited to, HER2-negative breast cancer, osteosarcoma, non-small cell lung, ovarian, prostate, head and neck, esophageal, gastric, pancreatic, colorectal, endometrial, or urothelial cancers. |
| <b>Nerlynx® (neratinib)</b>     | Except as noted above, Nerlynx® (neratinib) is considered investigational for the treatment of other conditions.  |
| <b>Injectable Drugs</b>         |   |
| <b>Herceptin® (trastuzumab)</b> | Except as noted above, Herceptin® (trastuzumab) is considered investigational for the treatment of conditions other than HER2-positive breast cancer including, but not   |



| Drug  | Investigational  |
|---|--|
|   | limited to, HER2-negative breast cancer, osteosarcoma, non-small cell lung, ovarian, prostate, head and neck, esophageal, gastric, pancreatic, colorectal, endometrial, or urothelial cancers.                                 |
| <b>Perjeta® (pertuzumab)</b>                | <b>All other uses of Perjeta® (pertuzumab) are considered investigational.</b>   |
| <b>Kadcyla™ (ado-trastuzumab emtansine)</b> | <b>All other uses of ado-trastuzumab emtansine are considered investigational, including but not limited to earlier stages of breast cancer, combination treatment with different agents, and treatment of gastric cancer.</b> |

## Coding

| Code         | Description   |
|--------------|---|
| <b>HCPCS</b> |   |
| J9306        | Injection, pertuzumab (Perjeta™), 1 mg                |
| J9354        | Injection, ado-trastuzumab emtansine (Kadcyla™), 1 mg |
| J9355        | Injection, trastuzumab (Herceptin®), 10 mg            |

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information

### HER2 Testing

Appropriate patient selection for trastuzumab therapy is predicated on detection of HER2 overexpression. HER2 overexpression should be assessed only by facilities with demonstrated proficiency in the specific assay being used. Unreliable results may result from improper assay performance. Several assays are commercially available to aid selection of patients for Trastuzumab therapy. These include the HercepTest™ and Pathway® HER2/neu, which are



immunohistochemical assays (IHC), and PathVysion® and HER2 FISH pharmDx™, which are fluorescence in situ hybridization assays (FISH).

### *Unresolved Issues*

As discussed in this policy, randomized clinical trials have consistently reported a beneficial effect of adjuvant trastuzumab in conjunction with adjuvant chemotherapy in patients with completely resected HER2-positive breast cancer.

### *Duration of Therapy*

While data support the use of adjuvant trastuzumab for a year, evidence is inadequate to determine if a second year of Trastuzumab therapy increases benefit. This comparison is a focus of the HERA trial, but data from its third arm, given 2 years of trastuzumab, are not yet available.

## **Starting Trastuzumab Long After Completing Adjuvant Chemotherapy**

Trastuzumab was rapidly integrated into the adjuvant therapy of patients with HER2-positive early-stage breast cancer. When the first interim results were reported in 2005, there was interest in offering Trastuzumab to patients who would otherwise meet criteria, but who had already completed adjuvant therapy prior to the announcement of trial results. This group of patients still has not been formally studied, but patients in the HERA trial started Trastuzumab a median 8 months after surgery. At the time, investigators suggested that patients who completed adjuvant chemotherapy within the prior 6 months might be considered reasonable candidates.

## **Concurrent Versus Sequential Therapy**

At present, data are inadequate to determine the optimal regimen of trastuzumab within the overall regimen of adjuvant therapy, specifically whether concurrent or sequential Trastuzumab is preferred. The NCCTG N9831 trial includes two arms given Trastuzumab, one concurrent with and the other following paclitaxel. Results for this comparison have not been published.



The FDA-approved label recommends that left ventricular ejection fraction (LVEF) should be measured before starting trastuzumab therapy, and shown to be within the treating institution's normal range. Continued therapy should depend on periodic monitoring (eg, at 3, 6, and 12 months) without an unacceptable decrease (eg, greater than 15%) from baseline LVEF.

Breast cancer patients considered for preoperative (neoadjuvant or primary systemic) chemotherapy may have early-stage disease, but larger tumors (stages IIA, IIB or operable T3N1M0), or may have locally advanced but non-metastatic (M0) disease.

## Safety Concerns with Ado-Trastuzumab Emtansine

Although there are no absolute contraindications to ado-trastuzumab emtansine, there are a number of additional safety considerations:

- Ado-trastuzumab emtansine is Pregnancy Category D, is associated with known gestational adverse effects, and should not be used in pregnant women. Effective contraception should be used during and for at least 6 months following treatment
- Increases in liver function enzymes are common. Dose modifications based on liver function tests are recommended
- Decreases in left ventricular ejection fraction have been noted. Inclusion criteria for the EMILIA trial included a LV ejection fraction of at least 50% or greater
- The safety and efficacy of ado-trastuzumab emtansine in pediatric patients has not been established
- Other safety concerns, which generally do not warrant a change in management, include infusion reactions, pulmonary toxicity, GI symptoms, and fatigue

## Benefit Application

State and federal mandates (eg, FEP) requiring coverage of FDA-approved drugs may supersede this policy.



## Description

The human epidermal growth factor receptor 2 (HER2) gene located on chromosome 17q, encodes a transmembrane ligand orphan receptor tyrosine kinase that amplifies the signal provided by other members of the HER family (HER1/EGFR, HER3, and HER4) by forming heterodimers with them. HER2 activation and dimerization causes alterations in several complex downstream-signaling cascades that are involved in regulation of cell growth, proliferation, migration, adhesion, and survival, and thus has been implicated in oncogenesis.

The HER2 gene is amplified and overexpressed in 20–30% of breast cancers, a finding which has been associated with more aggressive disease and higher relapse and mortality rates. HER2 is also overexpressed in other epithelial cancers, including ovarian, thyroid, lung, salivary gland, stomach, colon, and prostate, making it a logical target for antibody-mediated therapy.

Trastuzumab has only received U.S. Food and Drug Administration (FDA) marketing approval for specific patients with breast cancer. However, its activity has been investigated in the preoperative (neoadjuvant) setting for breast cancer, in combination with regimens besides those specified in the FDA-approved product label, and in a wide range of other types of cancer that overexpress HER2.

## Herceptin® (trastuzumab) in Breast Cancer

### *Metastatic*

The initial 1998 approval by the U.S. Food and Drug Administration (FDA) for trastuzumab in metastatic breast cancer was based on results from 2 pivotal clinical trials. In one trial, single-agent trastuzumab was given to women (n=222) who had received 1 or 2 courses of cytotoxic chemotherapy, yielding an objective response rate (ORR) of 15% and a median duration of response of 9.1 months.<sup>1</sup> In a second randomized trial (n=469), trastuzumab was evaluated as part of a first-line combination regimen consisting of either doxorubicin (A) plus cyclophosphamide (C) or paclitaxel (P).<sup>2</sup> The addition of trastuzumab to chemotherapy resulted in an increased response rate (50% vs. 32%, p<0.001), longer median response duration (9.1 vs. 6.1 months, p<0.001), and prolonged overall survival (OS) (25.1 months vs. 20.3, p=0.046) compared to chemotherapy alone. Because a significantly higher incidence of New York Heart Association (NYHA) class III or IV cardiotoxicity was reported in this trial among patients who received AC plus trastuzumab, compared to AC, paclitaxel/trastuzumab, or paclitaxel, the FDA





and others subsequently cautioned against using a regimen that combined trastuzumab with doxorubicin.<sup>3,4</sup>

Similar efficacy results have been subsequently reported with the combination of trastuzumab with docetaxel (D) in 188 patients with metastatic breast cancer.<sup>5</sup> Further studies of other trastuzumab combination regimens have included its use with capecitabine, vinorelbine, gemcitabine, and platinum salts, achieving response rates ranging from 27% to 86%.<sup>6,7</sup> These early studies also have shown that trastuzumab can be combined with non-approved chemotherapy regimens while adding little to the overall toxicity profile in the metastatic setting. Similarly, trastuzumab is being evaluated in combinations with hormonal modalities such as tamoxifen or aromatase inhibitors.

Kaufman and colleagues reported the results of the first randomized Phase III trial combining a hormonal agent (aromatase inhibitor anastrozole) and trastuzumab without chemotherapy.<sup>8</sup> Patients were postmenopausal with HER2 and hormone receptor-positive metastatic disease (patients with CNS metastases were excluded). Patients were randomized to receive trastuzumab plus anastrozole (n=103) or anastrozole alone (n=104). Baseline characteristics were balanced between the two groups. The primary endpoint was progression free survival (PFS), defined as the time from randomization and the date of disease progression or death. There were a total of 187 withdrawals from the trial treatment, most frequently due to progressive disease. In the anastrozole-only arm, 70% of the patients who experienced progressive disease subsequently crossed over to receive a trastuzumab containing regimen. Progression free survival was significantly improved in the trastuzumab plus anastrozole arm with a median PFS of 4.8 months (95% confidence interval [CI]: 3.7 to 7.0 months) versus 2.4 months (95% CI: 2.0 to 4.6 months) in the anastrozole-only arm (hazard ratio [HR] =0.63; 95%CI: 0.47-0.84; p=0.0016). Grade 3 and 4 adverse events were 23% and 5%, respectively, in the trastuzumab plus anastrozole arm, and 15% and 1% in the anastrozole-only arm.

Von Minckwitz and colleagues investigated whether trastuzumab should be given beyond disease progression in women with HER2-positive locally-advanced or metastatic breast cancer.<sup>9</sup> Patients were randomly assigned to chemotherapy (capecitabine) alone (n=78) or to capecitabine plus trastuzumab (n=78). Follow-up was 15.6 months, during which time there were 38 deaths in the capecitabine arm versus 33 in the capecitabine plus trastuzumab group. The primary end point in the study was time to progression, which was defined as the time period between randomization and documented disease progression or disease-related death. Median times to progression were 5.6 months in the capecitabine group and 8.2 months in the combined therapy group; hazard ratio 0.69 (95% CI: 0.48 to 0.97; p=0.0338). Differences in OS were not significant at 20.4 months (95% CI: 17.8 to 24.7) in the capecitabine group and 25.5 months (95% CI: 19.0 to 30.7) in the combined therapy group (p=0.257).



## Adjuvant

Results from randomized trials provide data on clinical outcomes of adjuvant trastuzumab therapy: the Breast Cancer International Research Group 006 trial (BCIRG 006, n=3,222)<sup>10</sup>; the Herceptin Adjuvant Trial (HERA, n=5,090)<sup>11</sup>; the North Central Cancer Treatment Group N9831 trial (NCCTG N9831, n=3,505)<sup>12</sup>; the North American National Surgical Adjuvant Breast and Bowel Project B31 trial (NSABP B31, n=2,030)<sup>13</sup>; and, the Finnish Herceptin Study (FinHer, n=232)<sup>14</sup>. All women enrolled in these studies tested positive for HER2 using either immunohistochemical assays (IHC) or fluorescence in situ hybridization assays (FISH) assays. There were important differences in patient characteristics, trial design, and implementation, as reviewed in depth elsewhere.<sup>7,15-18</sup>. The following table summarizes the design and results of those trials.

| Trial (ref)               | Tumor Characteristics   | Design  | Trastuzumab Schedule       | F/U (median, years) | DFS HR vs. controls [95% CI] (p)   | OS HR vs. controls [95% CI] (p)  |
|---------------------------|---|---|----------------------------|---------------------|--|--|
| BCIRG <sup>10</sup>       | node-positive, or high-risk node-negative                                 | AC→D<br>AC→DH<br>DCH                          | Q1wk w/CTx<br>Q3wk postCTx | 3                   | AC→DH:<br>0.61<br>[0.48-0.76]<br>( $< 0.0001$ )<br>DCH:<br>0.67<br>[0.54-0.83]<br>(0.0003) | AC→DH:<br>0.59<br>[0.42-0.85]<br>(0.004)<br>DCH:<br>0.66<br>[0.47-0.93]<br>(0.017) |
| HERA <sup>11</sup>        | node-positive, or node-negative with tumor $\geq 1$ cm                    | Accepted CTx<br>CTx→H (1 yr)<br>CTx→H (2 yrs) | Q3wk postCTx               | 2                   | 0.64<br>[0.43-0.57]<br>( $< 0.0001$ )  | 0.66<br>[0.47-1.23]<br>0.0115)   |
| NCCTG N9831 <sup>12</sup> | node-positive, or if node-negative, with primary tumor $> 1$ cm if ER/PR- | AC→P<br>AC→P→H<br>AC→PH                       | Q1wk w/CTx<br>Q1wk postCTx | 2                   | combined data:<br>0.48   | combined data:<br>0.67   |



| Trial (ref)             | Tumor Characteristics                                     | Design                     | Trastuzumab Schedule    | F/U (median, years) | DFS HR vs. controls [95% CI] (p) | OS HR vs. controls [95% CI] (p) |
|-------------------------|---|----------------------------|-------------------------|---------------------|----------------------------------|---------------------------------|
|                         | negative, or >2 cm if ER/PR-positive                      |                            |                         |                     | [0.39-0.59] (<0.0001)            | [0.48-0.93] (0.015)             |
| NSABP B31 <sup>13</sup> | node-positive   | AC→P<br>AC→PH              | Q1wk w/CTx Q1wk postCTx | 2                   |                                  |                                 |
| FinHer <sup>14</sup>    | node-positive, or node-negative and ≥2 cm and PR-negative | D or V→FEC<br>DH or VH→FEC | Q1wk w/CTx              | 3                   | 0.42 [0.21-0.83] (0.01)          | 0.41 [0.16-1.08] (0.07)         |

AC: doxorubicin + cyclophosphamide; CI: confidence interval; cm: centimeter; CTx: chemotherapy; DCH: docetaxel + carboplatin + trastuzumab; DFS: disease-free survival; ER/PR: estrogen receptor/progesterone receptor; FEC: 5-fluorouracil + epirubicin + cyclophosphamide; FU: follow-up; H: Herceptin® (trastuzumab); HR: hazard ratio; OS: overall survival; P: paclitaxel; Q: every; V: vinorelbine; w/: with.

Despite substantial differences in trial design and patient characteristics, the latest available data from adjuvant trials of trastuzumab demonstrate consistent, clinically significant improvements in DFS. The combined analysis of the NSABP B31, NCCTG N9831, BCIRG, and HERA trials shows significant improvement in OS versus controls in patients given adjuvant trastuzumab. Although only HERA reported that trastuzumab improved DFS in a subgroup with high-risk, node-negative disease, 3 other trials included similar patients and found better outcomes in the trastuzumab arm. While few patients were node negative in NCCTG N9831 and FinHer, 29% of each arm was node negative in BCIRG 006. Note that all trials excluded patients with small (<1 cm) node-negative tumors. Thus, there is no evidence that adjuvant trastuzumab benefits this subgroup of HER2-positive patients. The benefits of trastuzumab were independent of estrogen-receptor status or the type of prior chemotherapy. These data do not settle the issue of optimal timing and duration of trastuzumab therapy, but data from the FinHer study suggest that even a short course (9 weeks) may be beneficial in reducing the risk of recurrence and death in women with HER2-positive, early-stage disease. Furthermore, final results for the 2-year trastuzumab regimen arm in HERA are not yet available.

Grade III/IV congestive heart failure (CHF) or cardiac-related death for patients receiving trastuzumab-containing adjuvant regimens ranged from 0 (FinHer) to 4.1% (NSABP B31) overall, with age and baseline left-ventricular ejection fraction related to the risk for cardiac dysfunction. Concurrent use of trastuzumab and a taxane following 4 cycles of AC resulted in the highest



rates of CHF (1.5%, 2.4%, and 3.4% for the BCIRG, N9831, and B31 trials, respectively). Sequential administration of anthracyclines, taxanes, and trastuzumab resulted in CHF rates of 1.4% and 0.5% for the N9831 and HERA trials, respectively. The non-anthracycline arm of the BCIRG trial had the lowest rate (0.3%) of CHF. While the acceptable rate of cardiac events overall was likely related to rigorous monitoring during the trials, cross-trial comparisons and conclusions are difficult due to differences in definitions of cardiac events, evaluations for cardiac safety, analysis of cardiac endpoints (cumulative vs. overall incidence) and duration of follow-up.

## ***Neoadjuvant***

A randomized, controlled trial has been published on the benefits of adding trastuzumab to neoadjuvant chemotherapy.<sup>19</sup> The study sequentially administered two neoadjuvant chemotherapy regimens followed by surgery to breast cancer patients with stage II to IIIA disease, and compared paclitaxel (four 3-week cycles) followed by fluorouracil, epirubicin, and cyclophosphamide (FEC; four 3-week cycles) with versus without trastuzumab. A data monitoring committee ended the trial after investigators randomized 42 patients, when a requested (but unplanned) analysis showed pathologic complete response (pCR) rates of 25% in the arm without and 66.7% in the arm with trastuzumab. Approximately the same proportion of patients in each arm (52.6% without and 56.5% with trastuzumab) received breast-conserving surgery, but patient choice likely influenced these results. A subsequent report of the same study included longer follow-up for randomized patients, and additional nonrandomized patients.<sup>20</sup> Results showed pCR in 26.3% (95% CI: 9–51%) of 19 patients randomized to neoadjuvant chemotherapy without trastuzumab, 65.2% (95% CI: 43–84%) of 23 patients randomized to the same neoadjuvant regimen plus trastuzumab, and 54.5% (95% CI: 32.2–75.6%) of 22 consecutive nonrandomized patients also given the same regimen plus trastuzumab.<sup>20</sup> At a median follow-up of 36.1 months for randomized patients, 3 in the chemotherapy-only arm experienced recurrence (1 of whom died), and none in the arm with added trastuzumab.

Although few recurrences or deaths have occurred thus far in this terminated randomized, controlled trial, the 2-fold increase in pCR rate is unlikely to be a chance result.<sup>19,20</sup> Analyses from randomized, controlled trials<sup>21-23</sup> and single-arm studies<sup>24-26</sup> showed that patients with pCR after neoadjuvant chemotherapy (determined postoperatively) had significantly longer overall, disease-free, and/or recurrence-free survival than those who did not achieve pCR. This also was true when those who achieved pCR were compared with those who achieved clinically complete responses but were subsequently shown by postoperative pathology to have residual (microscopic) invasive disease. Thus, improving pCR rate by adding trastuzumab to neoadjuvant



chemotherapy for HER2 patients with high-risk, larger tumors predicts improved overall and disease-free survival.

Additional reasoning supports considering neoadjuvant trastuzumab medically necessary for HER2-positive patients undergoing neoadjuvant chemotherapy, even if the one available randomized, controlled trial did not show it increased the proportion of patients given breast-conserving surgery. When used to reduce risk of recurrence for patients with operable breast cancer, chemotherapy is either completed before surgery or not begun until after. Those given preoperative chemotherapy rarely receive additional chemotherapy after resection, unless their breast cancer recurs or progresses. Although hormone-receptor-positive patients given neoadjuvant chemotherapy are given tamoxifen or an aromatase inhibitor after resection, most HER2-positive patients are hormone-receptor negative and would not receive hormone therapy. Whether chemotherapy is used pre- or postoperatively, it is given for 18-24 weeks depending on the regimen and trastuzumab currently is given for a full year. Trastuzumab administration was initiated concurrently with chemotherapy in most trials on adjuvant therapy. Consequently, it seems reasonable to initiate trastuzumab with chemotherapy for HER2-positive patients receiving neoadjuvant chemotherapy.

## **Herceptin® (trastuzumab) in Non-Breast Cancer**

### ***Gastric Cancer***

One Phase II and one Phase III trial have been reported on the use of trastuzumab in advanced gastric cancer; the Phase II trial is published in abstract form only. Cortés-Funes and colleagues reported preliminary results of a Phase II study of 21 patients with advanced gastric cancer with overexpression/amplification of HER2.<sup>27</sup> Patients received trastuzumab in combination with chemotherapy (cisplatin) every 21 days until disease progression, unacceptable toxicity or withdrawal. Seventeen of the 21 patients were evaluable. Efficacy was reported as: 6 (35%) patients achieved response (1 CR, 5 PR), 3 (17%) had disease stabilization, 4 patients progressed and for 4 patients it was too early to report. The authors concluded that trastuzumab plus cisplatin is a well-tolerated regimen with promising activity in HER2/neu overexpressing gastric cancer.

Van Cutsem and colleagues reported the results of a Phase III, open-label, randomized, multicenter (122 centers in 24 countries) trial in which patients with HER2-positive, locally-advanced, recurrent, or metastatic gastroesophageal or gastric adenocarcinoma received chemotherapy consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin with or without trastuzumab.<sup>28</sup> Patients who received the trastuzumab were given it every three weeks



for 6 cycles, until disease progression. The primary endpoint of the study was overall survival; secondary endpoints were overall response rate (ORR), PFS, time to progression, duration of response and safety. Median follow-up was 18.6 months in the chemotherapy plus trastuzumab group and 17.1 months in the chemotherapy-alone group. Tumors from 3,807 patients were tested for HER2 status; 22.1% were positive. Five-hundred ninety-four patients were randomized to the 2 treatment arms. Median OS for the group that received trastuzumab compared to those that did not was 13.8 months (95% CI: 12-16) versus 11.1 months (95% CI: 10-13) ( $p=0.0046$ ; HR 0.74; 95%CI 0.60-0.91). ORR was 47.3% for those that received trastuzumab versus 34.5% for those that did not ( $p=0.0017$ ). Rates of overall grade 3 or 4 adverse events (201 [68%] versus 198 [68%]) and cardiac adverse events (17 [6%] versus 18 [6%]) did not differ between the chemotherapy and trastuzumab versus chemotherapy alone groups.

### ***Prostate Cancer***

Uncontrolled pilot studies have reported preliminary results for outcomes of trastuzumab combined with chemotherapy for advanced androgen-dependent or androgen-independent prostate cancer<sup>29,30</sup> that is positive for HER2 overexpression or amplification. A study of trastuzumab and docetaxel for HER2-positive prostate cancer was closed as not feasible, since only 7 of 100 patients screened had 2+ or 3+ HER2 expression by immunohistochemistry, as required for study eligibility.<sup>31</sup> Another study reported treatment with trastuzumab as a single agent demonstrated poor efficacy in 18 patients with advanced hormone-refractory prostate cancer.<sup>32</sup>

### ***Salivary Gland Cancer***

A study to evaluate the use of trastuzumab in salivary gland cancer was closed early after it was found that the majority of salivary gland tumors did not overexpress HER2.<sup>33</sup>

### ***Ovarian and Peritoneal Cancer***

A study of trastuzumab in patients with recurrent or refractory ovarian or primary peritoneal carcinoma found a low rate of clinical response to treatment.<sup>34</sup>



## ***Non-small Cell Lung Cancer***

Three reports were identified from phase II trials of trastuzumab plus chemotherapy to treat non-small cell lung cancer.<sup>35-37</sup> Each of these studies reported that the addition of trastuzumab did not improve outcomes.

A randomized Phase II comparison of docetaxel plus trastuzumab versus paclitaxel plus trastuzumab in chemotherapy-naive non-small cell lung cancer patients (n=65) reported no differences in objective response rates, median survival, or toxicity between arms.

## ***Esophageal Cancer***

Median OS was 24 months in an uncontrolled Phase I/II study (n=19) that combined trastuzumab with paclitaxel, cisplatin, and radiation for locally advanced, HER2 overexpressing esophageal cancer.

## ***Bladder and Kidney Cancer***

Two uncontrolled small series were also reported on trastuzumab for metastatic transitional cell cancer of the bladder (n=7) or bladder and renal pelvis (n=6).<sup>40,41</sup> A Phase II trial that treated 44 patients with HER2-positive, advanced urothelial carcinoma with a combination of trastuzumab, paclitaxel, carboplatin, and gemcitabine, showed 31 (70%) patients responded, including 5 complete and 26 partial responses. Median time to progression and survival were 9.3 and 14.1 months, respectively. However, the study lacked controls given the same chemotherapy without trastuzumab.

## **Summary**

Targeted therapy using trastuzumab against human epidermal growth factor receptor type-2 (HER2) has shown survival benefit for primary and metastatic breast cancer, and has become the accepted and usual therapy for patients with HER-2 positive breast cancer.

One Phase III trial has reported outcomes with the use of trastuzumab in advanced gastric or gastroesophageal cancer, with a 2 month OS benefit in the trastuzumab arm and no difference in severe adverse events between the group that received chemotherapy plus trastuzumab versus chemotherapy alone.



Studies examining the possible uses of trastuzumab in HER2-positive cancers other than breast and gastric/gastroesophageal cancers have consisted mainly of small uncontrolled series. For the most part, results have been disappointing, with little to no improvement in outcomes; studies have also suffered from the low percentage of HER2 overexpression in certain tumors.

## **Tykerb® (lapatinib)**

The efficacy and safety of Tykerb® (lapatinib) in combination with capecitabine in breast cancer were evaluated in a randomized, Phase III trial. Patients eligible for enrollment had HER2 (ErbB2) over-expressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab.

- Patients were randomized to receive either lapatinib 1,250 mg once daily (continuously) plus capecitabine 2,000 mg/m<sup>2</sup>/day on Days 1-14 every 21 days, or to receive capecitabine alone at a dose of 2,500 mg/m<sup>2</sup>/day on Days 1-14 every 21 days. The endpoint was time to progression (TTP). TTP was defined as time from randomization to tumor progression or death related to breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was discontinued. Three hundred ninety-nine (399) patients were enrolled in this study. The median age was 53 years and 14% were older than 65 years. Ninety-one percent (91%) were Caucasian. Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes, and trastuzumab. Independent assessment of patients showed a median time to progression of 27.1 weeks in the lapatinib group vs. 18.6 weeks in controls. Response rates were 23.7% (95% CI 18.0-30.3) and 13.9% (95% CI 9.5-19.5), respectively (HR 0.57, 95% CI 0.43-0.77, p=0.00013).

## **Kadcyla™ (ado-trastuzumab emtansine)**

Based on a literature search performed through April 2018, the evidence that was identified for this policy review consists of one RCT that was performed in support of application for FDA-approval, and two uncontrolled studies.





## ***Randomized, Controlled Trial***

The Phase III EMILIA trial (N=991) was a randomized, stratified, active- controlled, open-label trial conducted in 26 countries (27% US). Patients had unresectable, locally advanced or metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane. Median age was 53 years, approximately 37% of patients had three or more metastatic sites, and 68% had visceral disease involvement. Patients were stratified (by world region, number of prior chemotherapy regimens for advanced disease, and visceral disease involvement) and randomized to one of two treatment groups: intravenous infusions of ado-trastuzumab emtansine 3.6 mg/kg every 21 days or self- administered oral lapatinib 1250 mg daily plus oral capecitabine 1000 mg/m<sup>2</sup> every 12 hours for the first 14 days of each 21-day treatment cycle. Potential bias introduced by the open-label trial design was minimized by assessor blinding of PFS and tumor response endpoints and by the use of an easily measured endpoint, OS.

Primary efficacy outcomes were PFS by independent review committee and overall survival (OS). PFS was 9.6 months in the ado-trastuzumab emtansine group and 6.4 months in the lapatinib+capecitabine group (hazard ratio [HR] 0.65 [95% CI: 0.55, 0.77]). Statistically nonsignificant differences in PFS were found in patients without visceral involvement and in patients from Asia and other parts of the world (stratified subgroups) and in patients 65 to 74 years of age and patients without measurable disease at baseline (prespecified subgroups). At a median follow-up of approximately 19 months, an interim analysis of OS crossed the pre-determined stopping boundary, and the trial was discontinued. OS was 30.9 months in the ado-trastuzumab emtansine group and 25.1 in the lapatinib+capecitabine group (HR 0.68 [95% CI: 0.55, 0.85]).

## ***Uncontrolled Trials***

Two single-arm, open-label, Phase II studies conducted in the US enrolled patients with HER2 positive metastatic breast cancer and measurable disease. In TDM4374g (N=110), patients were previously treated with trastuzumab, lapatinib, a taxane, an anthracycline, and capecitabine. Ninety-eight percent of patients were female, median age was 53 years, 74% of patients had three or more metastatic sites, and patients had received a median of 7 systemic treatments for metastatic disease. In TDM4258g (n=112), patients were previously treated with HER2-directed therapy (trastuzumab or lapatinib). Median age was 55 years, 75% of patients had three or more metastatic sites, and patients had received a median of 5 systemic treatments for metastatic disease. All patients in both studies received ado-trastuzumab emtansine 3.6 mg/kg IV every 3 weeks with dose modifications for adverse events.



Objective response rate (ORR, defined as complete responses plus partial responses) by independent radiologic facility (IRF) was the primary efficacy outcome in both studies. In TDM4374g (more pre-treatment), ORR was 35% (95% confidence interval [CI]: 26, 44). In TDM4258g (less pre-treatment), ORR was 26% (95% CI: 18, 34). There were no complete responses. Median progression-free survival (PFS), a secondary outcome, was 6.9 months (95% CI: 4.2, 8.4) in TDM4374g and 4.6 months (95% CI: 3.9,8.6) in TDM4258g.

### ***Off-Label Use***

Conference abstracts have presented results of several Phase I and Phase II studies of ado-trastuzumab emtansine for off-label uses. The main categories for off-label uses are for breast cancer at earlier stages or in various combination therapies for breast cancer, and for use in non-breast cancers.

### ***Earlier Stages of Breast Cancer***

The MARIANNE trial, currently in progress, is a Phase III, three-arm trial comparing ado-trastuzumab emtansine, ado-trastuzumab emtansine plus pertuzumab, and trastuzumab plus a taxane for first-line treatment of metastatic breast cancer. GDC-0941 is an oral inhibitor of a downstream intracellular pathway regulated by HER2. Constitutive activation of this pathway is thought to contribute to trastuzumab insensitivity in HER2-positive breast cancer. A Phase Ib dose escalation study of this combination in patients with HER2-positive breast cancer who progressed on prior trastuzumab therapy is currently in progress.

Additional indications being studied include initial treatment of metastatic breast cancer, in combination with pertuzumab and/or paclitaxel for previously treated metastatic disease, or in patients previously treated with systemic chemotherapy.

### ***Other Cancer Types***

In preclinical studies of gastric cancer, ado-trastuzumab emtansine has shown efficacy. An ongoing Phase I study is assessing the combination of ado-trastuzumab emtansine plus capecitabine in patients with metastatic HER2-positive gastric cancer. A Phase III trial (N=412) comparing two different doses of ado-trastuzumab emtansine (3.6 mg/kg every three weeks or 2.4 mg/kg weekly) to standard taxane therapy in patients with HER2- positive advanced gastric



cancer who experienced disease progression during or after first-line therapy is currently in progress.

## 2013 National Comprehensive Cancer Network (NCCN) Compendium Recommendations

### *Trastuzumab*

The current NCCN Compendium recommends the use of trastuzumab as follows:

#### **Breast Cancer**

##### ***Neoadjuvant therapy***

Preoperative therapy for patients with HER2-positive stage IIA, IIB, or T3, N1, M0 disease who desire breast preservation and fulfill criteria for breast-conserving surgery except for tumor size or for locally advanced disease (stage IIIA, IIIB, or IIIC) (Category 1):

- Concurrently with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen as preferred regimen
- In TCH (docetaxel, carboplatin, and trastuzumab) regimen as preferred regimen
- In combination with docetaxel followed by FEC/CEF (fluorouracil, epirubicin, and cyclophosphamide) regimen
- In combination with docetaxel following AC regimen
- In combination with paclitaxel followed by FEC/CEF (fluorouracil, epirubicin, and cyclophosphamide) regimen with trastuzumab

##### ***Adjuvant therapy***

HER2-positive, stage I, IIA, IIB, or T3, N1, M0 disease (ductal, lobular, mixed, or metaplastic histologies) that is pN0 (tumor greater than 0.5 cm), pN1mi, or node-positive or for locally advanced disease (stage IIIA, IIIB, or IIIC) (Category 1 for tumors > 1 cm; 2A if smaller):



- Concurrently with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen as preferred regimen
- In TCH (docetaxel, carboplatin, and trastuzumab) regimen as preferred regimen
- In combination with docetaxel followed by FEC/CEF (fluorouracil, epirubicin, and cyclophosphamide) regimen
- In combination with docetaxel following AC regimen

### **Recurrent or Stage IV disease**

Used in combination with aromatase inhibition for the treatment of recurrent or stage IV estrogen receptor-positive, human epidermal growth factor receptor 2-positive disease in postmenopausal women\* who have received no prior endocrine therapy within one year. (Category 2A)

### **Male Breast Cancer**

Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis. (Category 2A)

### **Hormone Receptor-Negative or Endocrine Refractory Disease**

HER2-positive recurrent or metastatic breast cancer that is hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory as:

- Preferred first-line therapy in combination with pertuzumab with docetaxel or paclitaxel (Category 1)
- First-line therapy in combination with docetaxel, vinorelbine, or capecitabine or with paclitaxel with or without carboplatin (Category 2A)
- Treatment for trastuzumab-exposed HER2-positive disease in combination with lapatinib without cytotoxic therapy (Category 2A)



- May be considered in combination with pertuzumab with or without cytotoxic therapy (eg, vinorelbine or taxane) for one line of therapy beyond first-line therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab (Category 2A).

## **Gastric Cancer**

Palliative therapy for patients with Karnofsky performance score  $\geq 60\%$  or ECOG performance score  $\leq 2$  in combination with systemic chemotherapy for the treatment of patients with advanced HER2-neu protein overexpressing gastric, esophageal or esophagogastric junction adenocarcinoma. (Category 1 for combination with cisplatin and fluorouracil or capecitabine for first-line therapy; 2A for combination with cisplatin and fluorouracil or capecitabine for second-line therapy; 2B otherwise.)

As of July 2013, use of trastuzumab has not been addressed the NCCN Compendium for other malignancies, including: osteosarcoma, ovarian, prostate, head and neck, pancreatic, colon, rectal, endometrial, urothelial or non-small cell lung cancers.

## ***Tykerb® (lapatinib)***

The current NCCN Compendium recommends the use of Tykerb® (lapatinib) as follows:

### **Breast Cancer**

Used in combination with aromatase inhibition for the treatment of recurrent or stage IV estrogen receptor-positive, human epidermal growth factor receptor 2-positive disease in postmenopausal women\* who have received no prior endocrine therapy within one year. Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis. (Category 2A)

Used in combination with trastuzumab (without cytotoxic therapy) or capecitabine for human epidermal growth factor receptor 2-positive recurrent or metastatic trastuzumab-exposed disease. (Category 2A)

Consider for treatment in combination with capecitabine for recurrent brain metastases if active against primary tumor (breast). (Category 2A)



## ***Nerlynx® (neratinib)***

In the multicenter, randomized, double-blind, placebo-controlled phase-3 ExteNET, the efficacy of 12 months of neratinib were evaluated in stage 1-3 HER-2 positive breast cancer. Patients received either neratinib 240mg daily for 12 months or a matching placebo following after trastuzumab-based adjuvant therapy. The results reported that at 2-year follow-up, the neratinib group had significantly fewer invasive disease-free survival events vs. the placebo group (70 vs. 109 events, HR 0.67, P=0.0091). The disease-free survival events include: local/regional invasive recurrence and/or distant recurrence to at least one other location/tissue, and death. The neratinib group also had higher 2-year invasive disease-free survival rate (93.9% vs. 91.6%, P=0.0091), higher 2-year rates for distant disease-free survival (95.1% vs. 93.7%), and longer time to distant recurrence (95.4% vs. 93.9%). Overall survival data were not mature but would continue to be monitored. Other trials included in the support for FDA-approved labeling are two phase-2 studies to establish the efficacy and safety of neratinib as compared to the current standard therapy (neratinib + paclitaxel vs. trastuzumab + paclitaxel, neratinib monotherapy vs. lapatinib + capecitabine) in HER2-positive BC.

## ***Other HER2 Inhibitors***

Tykerb® (lapatinib) is a small molecule 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor Type 2 (HER2 [ErbB2]) receptors. Lapatinib inhibits ErbB-driven tumor cell growth in vitro and in various animal models.

Lapatinib is indicated for use in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

Perjeta® (pertuzumab) is a HER dimerization inhibitor recently approved by the FDA for use in combination with trastuzumab and docetaxel in patients with HER2-positive metastatic cancer who are treatment naïve or whose disease has recurred after adjuvant therapy.

Kadcyla™ (ado-trastuzumab emtansine), also known as trastuzumab-DM1 or T-DM1, is an antibody-drug conjugate comprising trastuzumab and emtansine (DM1). It is a HER2 antagonist that is intended as treatment for patients with breast cancers that overexpress HER2, and it may also have applications for other HER-2 positive malignancies. 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 linkage. T-DM1 binds HER2 with an affinity comparable to 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 (described above). Death of HER2-expressing cells therefore results from effects of both active moieties of ado-trastuzumab emtansine.

## **2012 Update**

Updated to include new data on expanded indications of trastuzumab and addition of criteria for pertuzumab.

## **2013 Update**

Updated to include ado-trastuzumab emtansine, which was recently approved by the FDA, and current NCCN Compendium recommendations.

## **2014 Update**

Updated to include current NCCN Compendium recommendations for use of trastuzumab outside of breast cancer.

## **2015 Update**

No information was found that would prompt a change in policy statements.

## **2018 Update**

Updated per labeled indications and literature search from 1/1/17 through 4/1/18.



## Regulatory Status

Herceptin® (trastuzumab) is a humanized monoclonal antibody against the extracellular domain of HER2. Trastuzumab has received FDA marketing approval for treatment of HER2-positive breast cancer in both the adjuvant and metastatic settings. It first received FDA approval in September 1998 for use in metastatic breast cancer, as a first-line therapy in combination with paclitaxel and as a single agent in second- and third-line therapy.

In November 2006, trastuzumab received FDA marketing approval as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel (AC→P) for the adjuvant treatment of HER2-positive, node-positive early stage breast cancer.

In January 2008, FDA granted marketing approval for trastuzumab as a single agent for the adjuvant treatment of early stage HER2-positive node-positive breast cancer or node-negative (ER/PR-negative or with one high-risk feature) disease following multi-modality, anthracycline-based therapy. Trastuzumab also was approved to be administered as a single agent in an every-3-week dosing schedule for 1 year.

In May 2008, the FDA approved two new trastuzumab containing regimens for the adjuvant treatment of early-stage HER2-positive node-positive or node-negative (ER/PR-negative or with one high-risk feature) breast cancer. The first regimen is in combination with docetaxel and carboplatin (also known as TCH for Taxotere®, carboplatin, and Herceptin®), which does not contain an anthracycline (doxorubicin) component. The second is part of a treatment regimen containing anthracycline (doxorubicin), cyclophosphamide, and docetaxel (AC-TH).

## References

1. Cobleigh MA, Vogel CL, Tripathy D et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999; 17(9):2639-48.
2. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; 344(11):783-92.
3. Seidman A, Hudis C, Pierrri MK et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; 20(5):1215-21.
4. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer* 2002; 95(7):1592-600.
5. Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005; 23(19):4265-74.





6. Jackisch C. HER-2-positive metastatic breast cancer: optimizing trastuzumab-based therapy. *Oncologist* 2006; 11(suppl 1):34-41.
7. Demonty G, Bernard-Marty C, Puglisi F et al. Progress and new standards of care in the management of HER-2 positive breast cancer. *Eur J Cancer* 2007; 43(3):497-509.
8. Kaufman B, Mackey JR, Clemens MR et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol* 2009; 27(33):5529-37.
9. von Minckwitz G, du Bois A, Schmidt M et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German breast group 26/breast international group 03-05 study. *J Clin Oncol* 2009; 27(12):1999-2006.
10. Slamon D, Eiermann W, Robert N et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab in HER-2 positive early breast cancer patients: BCIRG 006 study. *Breast Cancer Res Treat* 2005; 94:S5. Abstract 1.
11. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; 353(16):1659-72.
12. Tan-Chiu E, Yothers G, Romond E et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; 23(31):7811-9.
13. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; 353(16):1673-84.
14. Joensuu H, Kellokumpu-Lehtinen PL, Bono P et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006; 354(8):809-20.
15. Baselga J, Perez EA, Pienkowski T et al. Adjuvant trastuzumab: a milestone in the treatment of HER-2-positive early breast cancer. *Oncologist* 2006; 11(suppl 1):4-12.
16. Engel RH, Kaklamani VG. HER-2-positive breast cancer: current and future treatment strategies. *Drugs* 2007; 67(9):1329-41.
17. Nanda R. Targeting the human epidermal growth factor receptor 2 (HER2) in the treatment of breast cancer: recent advances and future directions. *Rev Recent Clin Trials* 2007; 2(2):111-6.
18. Viani GA, Afonso SL, Stefano EJ et al. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. *BMC Cancer* 2007; 7:153-63.
19. Buzdar AU, Ibrahim NK, Francis D et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol* 2005; 23(16):3676-85.
20. Buzdar AU, Valero V, Ibrahim NK et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. *Clin Cancer Res* 2007; 13(1):228-33.
21. Fisher B, Bryant J, Wolmark N et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998; 16(8):2672-85.
22. Wolmark N, Wang J, Mamounas E et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr* 2001; 30:96-102.
23. Bear HD, Anderson S, Smith RE et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2006; 24(13):2019-27.



24. Feldman LD, Hortobagyi GN, Buzdar AU et al. Pathological assessment of response to induction chemotherapy in breast cancer. *Cancer Res* 1986; 46(5):2578-81.
25. Kuerer HM, Newman LA, Smith TL et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 1999; 17(2):460-9.
26. Hurley J, Doliny P, Reis I et al. Docetaxel, cisplatin and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. *J Clin Oncol* 2006; 24(12):1831-8.
27. Cortés-Funes H, Rivera F, Alés I et al. Phase II of trastuzumab and cisplatin in patients with advanced gastric cancer with HER2/neu overexpression/amplification. 2007 ASCO Annual Meeting Proceedings. *J Clin Oncol* 2007; 25(18 suppl):abstract 4613.
28. Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for the treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (TOGA): a phase III, open-label, randomized controlled trial. *Lancet* 2010; 376(9742):687-97.
29. Small EJ, Bok R, Reese DM et al. Docetaxel, estramustine, plus trastuzumab in patients with metastatic androgen-independent prostate cancer. *Semin Oncol* 2001; 28(4 suppl 15):71-6.
30. Morris MJ, Reuter VE, Kelly WK et al. HER-2 profiling and targeting in prostate carcinoma. *Cancer* 2002; 94(4):980-6.
31. Lara PN Jr, Chee KG, Longmate J et al. Trastuzumab plus docetaxel in HER-2/neu-positive prostate carcinoma: final results from the California Cancer Consortium Screening and Phase II Trial. *Cancer* 2004; 100(10):2125-31.
32. Ziada A, Barqawi A, Glode LM et al. The use of trastuzumab in the treatment of hormone refractory prostate cancer; phase II trial. *Prostate* 2004; 60(4):332-7.
33. Haddad R, Colevas AD, Krane JF et al. Herceptin in patients with advanced or metastatic salivary gland carcinomas. A phase II study. *Oral Oncol* 2003; 39(7):724-7.
34. Bookman MA, Darcy KM, Clarke-Pearson D et al. Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: a phase II trial of the Gynecologic Oncology Group. *J Clin Oncol* 2003; 21(2):283-90.
35. Zinner RG, Glisson BS, Fossella FV et al. Trastuzumab in combination with cisplatin and gemcitabine in patients with Her2-overexpressing, untreated, advanced non-small cell lung cancer: report of a phase II trial and findings regarding optimal identification of patients with Her2-overexpressing disease. *Lung Cancer* 2004; 44(1):99-110.
36. Langer CJ, Stephenson P, Thor A et al. Trastuzumab in the treatment of advanced non-small-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group study 2598. *J Clin Oncol* 2004; 22(7):1180-7.
37. Gatzemeier U, Groth G, Butts C et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. *Ann Oncol* 2004; 15(1):19-27.
38. Krug LM, Miller VA, Patel J et al. Randomized phase II study of weekly docetaxel plus trastuzumab versus weekly paclitaxel plus trastuzumab in patients with previously untreated advanced nonsmall cell lung carcinoma. *Cancer* 2005; 104(10):2149-55.
39. Safran H, DiPetrillo T, Akerman P et al. Phase I/II study of trastuzumab, paclitaxel, cisplatin, and radiation for locally advanced, HER2 overexpressing, esophageal adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2007; 67(2):405-9.
40. Salzberg M, Borner M, Bauer JA et al. Trastuzumab (Herceptin®) in patients with HER-2-overexpressing metastatic or locally advanced transitional cell carcinoma of the bladder: report on 7 patients. *Eur J Cancer* 2006; 42(15):2660-1.
41. Peyromaure M, Scotte F, Amsellem-Ouazana D et al. Trastuzumab (Herceptin) in metastatic transitional cell carcinoma of the urinary tract: report on six patients. *Eur Urol* 2005; 48(5):771-8.
42. Hussain MH, MacVicar GR, Petrylak DP et al. Trastuzumab, paclitaxel, carboplatin, and gemcitabine in advanced human epidermal growth factor receptor-2/neu-positive urothelial carcinoma: results of a multicenter phase II National Cancer Institute trial. *J Clin Oncol* 2007; 25(16): 2218-24.



43. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:26:2733-2743.
44. Ravaud A, Gardner J, Hawkins R et al. Efficacy of lapatinib in patients with high tumor EGFR expression: results of a phase III trial in advanced renal cell carcinoma (RCC). *J Clin Onc* 2004;24(18S):4502.
45. Prescribing information for Tykerb. GlaxoSmithKline, Inc., Research Triangle Park, NC. April 2010.
46. Blackwell KL, Kaplan EH, Franco SX et al. A phase II, open label, multicenter study of GW572016 in patients with trastuzumab refractory metastatic breast cancer. *J of Clin Onc* 2004;22(14S):3006.
47. Lin NA, Carey LA, Liu MC et al. Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancer. *J Clin Onc* 2006;24(18S):503.
48. Gomez HL, Chavez MA, Doval DC et al. A phase II randomized trial using the small molecule tyrosine kinase inhibitor lapatinib as a first-line treatment in patients with FISH positive advanced or metastatic breast cancer. *J Clin Onc* 2005;23(16S):3046.
49. Spector HL, Blackwell K, Jurly J et al. EGF103009, a phase II trial of lapatinib monotherapy in patients with relapse/refractory inflammatory breast cancer (IBC): clinical activity and biologic predictors of response. *J Clin Onc* 2006;24(18S):502.
50. Perez E, Byrne J, Rappold E et al. Cardiac safety experience in 3558 patients treated with lapatinib. *ESMO*. 2006.
51. Nelson MH, Dolder CR. Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors. *Ann Pharmacotherapy* 2006;40:261-269.
52. Baselga J, Cameron D, Miles D, et al. Objective response rate in a phase II multicenter trial of pertuzumab (P), a HER2 dimerization inhibiting monoclonal antibody, in combination with trastuzumab (T) in patients (pts) with HER2-positive metastatic breast cancer (MBC) which has progressed during treatment with T. *J Clin Oncol*. 2007;25(18 suppl):ASCO Abstract #1004. [http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18\\_suppl.1004](http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.1004) Accessed May 2018.
53. Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. E-pub Date: 2011. DOI # 10.1056/NEJMoa1113216.
54. Baselga J, Fumoleau P, Verma S, et al. A phase II trial of trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer that had progressed during trastuzumab therapy: Full response data. *Ann Oncol*. 2008;19(suppl 8):viii65. *ESMO Abstract #140P*.
55. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol*. 2010;28:1138-1144.
56. Baselga J, Imadalou K, Paton V, et al. Efficacy, safety and tolerability of dual monoclonal antibody therapy with pertuzumab + trastuzumab in HER2+ metastatic breast cancer patients previously treated with trastuzumab. *Cancer Res*. 2009;69(2 suppl 1):SABCS Abstract #3138. [http://cancerres.aacrjournals.org/content/69/2\\_Supplement/3138.abstract](http://cancerres.aacrjournals.org/content/69/2_Supplement/3138.abstract) Accessed May 2018.
57. Baselga J, Kim S-B, Im S-A, et al. A phase III, randomized, double-blind, placebo-controlled registration trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in patients with previously untreated HER2-positive metastatic breast cancer (CLEOPATRA). *Cancer Res*. 2011;71(24 suppl):112s. *SABCS Abstract #S5-5*.
58. Cortes J, Gelmon K, Fumoleau P, et al. Phase II evaluation of the efficacy and safety of trastuzumab plus pertuzumab therapy in patients with HER2-positive metastatic breast cancer that had progressed during trastuzumab treatment. *Eur J Cancer Suppl*. 2008;6:217. *EBCC Abstract #566*.
59. Suter T, Brammer M, Ross G, et al. Pooled analysis of cardiac safety in patients treated with pertuzumab. *Cancer Res*. 2009;69(24 suppl 3):SABCS Abstract #5088. [http://cancerres.aacrjournals.org/content/69/24\\_Supplement/5088](http://cancerres.aacrjournals.org/content/69/24_Supplement/5088) Accessed May 2018.
60. Verma S, Dieras V, Gianni L et al. EMILIA: A phase III, randomized, multicenter study of trastuzumab-DM1 (T-DM1) compared with lapatinib (L) plus capecitabine (X) in patients with HER2-positive locally advanced or metastatic breast cancer (MBC) and previously treated with a trastuzumab-based regimen. *J Clin Oncol* 2011; 29(15 suppl 1)abstract.



61. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012; 367(19): 1783-1791. Krop IE, LoRusso P, Miller KD et al. A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2012; 30(26):3234-41.
62. Burris HA, 3rd, Rugo HS, Vukelja SJ et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol* 2011; 29(4):398-405.
63. NCCN Drugs and Biologics Compendium 2013. Available at: [https://www.nccn.org/professionals/drug\\_compendium/default.aspx](https://www.nccn.org/professionals/drug_compendium/default.aspx) Accessed May 2018.
64. Capuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). *J Thoracic Oncol* 2007;2:423-429.
65. Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol* 2013;31:1997-2003.
66. 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. *Journal of Clinical Oncology* 35, no. 15\_suppl (May 2017) 8510.

## History

| Date     | Comments  |
|----------|---|
| 09/07/99 | Add to Prescription Drug Section - New medical policy.  |
| 01/14/03 | Replace Policy - Policy updated with new references; policy statement unchanged   |
| 03/08/05 | Replace Policy - Policy reviewed; references added; current clinical trials and NCCN guidelines information added; policy statement unchanged.  |
| 08/09/05 | Policy replaces BC.5.01.12 - New PR Policy. Policy statement changed to consider off-label uses of Trastuzumab medically necessary in tx of all stages of breast cancer with over-expressed HER-2/neu protein, or that are FISH positive. Trastuzumab to continue to be investigational for other malignancies. |
| 02/06/06 | Codes updated - No other changes.   |
| 06/16/06 | Update Scope and Disclaimer - No other changes.   |
| 08/08/06 | Replace Policy - Policy reviewed with literature search; no change to policy statement.   |
| 10/09/07 | Replace Policy - Policy reviewed with literature search. New FDA labeled indication noted in the Description. References added. No change to policy statement.  |
| 10/14/08 | Replace Policy - Policy reviewed with literature search. Policy no longer addresses only off-label uses. Renamed "HER2 Inhibitors". Tykerb added as medically necessary when criteria are met. References and code added. Policy guidelines now state that HER2 overexpression testing is required.             |
| 12/08/09 | Replace Policy - Policy reviewed with literature search. New indication: Herceptin is   |



| Date     | Comments   |
|----------|--|
|          | now considered medically necessary for gastric cancer.   |
| 05/11/10 | Replace Policy - Herceptin, previously considered investigation for esophageal cancer, is now considered medically necessary.  |
| 05/10/11 | Replace Policy - Policy rewritten and revised. Title changed from "HER-2 Inhibitors" to "Trastuzumab and Other HER2 Inhibitors." Components of BC.5.01.12 Trastuzumab incorporated in large part into the policy with the following variations: Lapatinib indications added. ICD-10 codes added to policy.   |
| 12/19/11 | Related Policies section updated; policy 2.04.76 added.  |
| 06/26/12 | Replace policy. Policy reviewed with literature search; no change in policy statements.  |
| 09/21/12 | Coding Section updated – ICD-10 codes are now effective 10/01/2014.  |
| 11/13/12 | Replace policy. Policy updated with new data on expanded indications of trastuzumab, coverage is expanded for adjuvant treatment of HER2 positive as either part of several different combination therapy regimens or as a single agent following prior chemotherapy; addition of criteria for pertuzumab; and treatment of HER2 positive <i>metastatic</i> breast cancer in either combination therapy or as a single agent. A medically necessary policy statement has been added for pertuzumab in the treatment of previously untreated HER2-positive breast cancer or recurrent breast cancer after adjuvant therapy, when used in combination with trastuzumab and docetaxel; all other uses are now indicated as investigational. |
| 01/04/13 | Minor update. For clarification and improved readability, the medically necessary policy statement for Pertuzumab now appears within the section addressing HER-2 positive breast cancer. No changes have been made to the policy.   |
| 07/08/13 | Replace Policy. Added Policy statements and Policy Guidelines information for ado-trastuzumab emtansine. Added clinical trial info for ado-trastuzumab emtansine to the Rationale section. Updated with current NCCN for all 3 drugs.  |
| 03/27/14 | Coding update; HCPCS code J9306, effective 1/1/14, added to the policy.  |
| 11/10/14 | Annual Review. Updated to include two medically necessary statements from current NCCN Compendium recommendations for use of trastuzumab outside of breast cancer. Codes removed with the exception of HCPCS J0306 and J9355; others are not utilized in adjudication of the policy.   |
| 02/10/15 | Minor update. Clarification added to the medically necessary policy statement for pertuzumab: This includes use as adjuvant therapy, neoadjuvant therapy, and treatment of metastatic disease.   |
| 09/08/15 | Annual Review. Policy updated with literature review. No change in policy statements.  |
| 01/28/16 | Minor update. Added HCPCS code J9354, effective 1/1/16, to the coding table.   |
| 10/01/16 | Annual Review, approved September 13, 2016. Clarification on the criteria for pertuzumab (addition of paclitaxel).   |



| Date     | Comments   |
|----------|--|
| 06/01/17 | Annual Review, approved May 23, 2017. A statement outlining the length of therapy for initial approval has been added to the policy. |
| 10/01/17 | Interim Review, approved September 21, 2017. Added criteria for Nerlynx.   |
| 02/01/18 | Interim Review, approved January 9, 2018. Revised Nerlynx ® (neratinib) criteria to reflect NCCN guidelines.                         |
| 04/01/18 | Interim Review, approved March 13, 2018. Updated Perjeta criteria to include expanded FDA label indication.                          |
| 06/01/18 | Annual Review, approved May 3, 2018. Updated references and per labeled indications and literature search, April 2018.               |

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.



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Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals  
PO Box 91102, Seattle, WA 98111  
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357  
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services  
200 Independence Avenue SW, Room 509F, HHH Building  
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)  
Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

**Getting Help in Other Languages**

**This Notice has Important Information.** This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

**አማርኛ (Amharic):**

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀዳሾች ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

**العربية (Arabic):**

يحتوي هذا الإشعار على معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تزيد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تاريخ معينه للحفاظ على تغطيتك الصحية أو المساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

**中文 (Chinese):**

**本通知有重要的訊息。**本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

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**Beeksisni kun odeeffannoo barbaachisaa qaba.** Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

**Français (French):**

**Cet avis a d'importantes informations.** Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

**Kreyòl ayisyen (Creole):**

**Avi sila a gen Enfòmasyon Enpòtan ladann.** Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

**Deutsche (German):**

**Diese Benachrichtigung enthält wichtige Informationen.** Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

**Hmoob (Hmong):**

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**Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion.** Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenna coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-ato wenna tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

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