BlueCross BlueShield of Alabama

Name of Policy:
Herceptin® (trastuzumab)

Policy #: 657
Category: Pharmacology
Effective Date: April 8, 2017
Latest Review Date: February 2017

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

In certain cancers, the human epidermal growth factor receptor 2 (HER2) gene is amplified and overexpressed. Trastuzumab (Herceptin) is a humanized monoclonal antibody, HER2 receptor antagonist, used for the treatment of various cancers including breast and metastatic gastric or gastroesophageal junction adenocarcinoma.

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 also may be 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 received U.S. Food and Drug Administration (FDA) marketing approval only for specific patients with breast cancer and gastric or gastroesophageal junction adenocarcinoma. 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 over express HER2.

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

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 and HER2 overexpression should be confirmed using FDA approved tests for the specific tumor types. It is recommended that FDA approved tests are used due to differences in tumor histopathology. Improper assay performance may yield unreliable results. Current FDA approved HER2 overexpression tests include immunohistochemical assays (IHC) and in situ hybridization assays (FISH).

Policy:

Effective for dates of service on or after April 8, 2017

Breast Cancer

Herceptin® (trastuzumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the **treatment of patients with breast cancer** who meet-criteria (A) **AND one or more** of the indications listed in (B):

A. Individuals whose breast tumors 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/CEP 17 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

B. Individuals meet **one or more** of the following indications:
    1. As a component of neoadjuvant therapy prior to surgical treatment;**or**
    2. As adjuvant treatment of breast cancer to complete a 12-month (52 weeks) course of trastuzumab; **or**
    3. In combination therapy with pertuzumab when the criteria to treat breast cancer in Medical Policy for Pertuzumab (Perjeta®) are met; **or**
    4. In combination therapy with lapatinib as a treatment of **metastatic breast cancer** when **both** of the following criteria are met:
        a. Individual has received or is receiving trastuzumab-based therapy; **and**
        b. Disease has progressed on or after trastuzumab therapy; **or**
    5. As treatment of metastatic breast cancer in combination therapy, or as a single agent <u>following prior treatment with one or more chemotherapy agents</u>; **or**
    6. ~~or in combination with chemotherapy (any chemotherapy approved for use in breast cancer, except when the combination is addressed in another medically necessary or investigational and not medically necessary statement below) either in treatment-naive individuals or individuals already receiving chemotherapy~~.

Gastric, Esophageal and Gastroesophageal Adenocarcinoma
Herceptin®(trastuzumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for individuals with **locally advanced or metastatic gastric, esophageal or gastroesophageal (GE) junction adenocarcinoma** who meet criteria: (A) **AND** in addition, **BOTH** of the criteria listed in (B) below:

A. Individuals whose tumors have HER2 protein overexpression documented by **one** of the following:
    1. Immunohistochemistry (IHC) 3+; **or**
    2. Fluorescent in situ hybridization (FISH) HER2 gene copy is greater than 6; **or**
    3. FISH ratio of HER2 gene/chromosome 17 ratio is greater than or equal to 2.0;

    AND
B. Individuals meet the following criteria:
    1. Used in combination treatment <u>with cisplatin plus capecitabine or 5-fluorouracil</u>; **and**
    2. Trastuzumab is used in only one line of therapy.

Except as noted above, **Herceptin® (trastuzumab) does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for the treatment of all other conditions including**,** but not limited to**,** HER2-negative breast cancer, and the following cancers which may be HER2-positive: osteosarcoma, non-small-cell lung, ovarian,

prostate, head and neck, esophageal (except as noted above), gastric (except as noted above), pancreatic, colorectal, endometrial, or urothelial.

Effective for dates of service September 1, 2015 through April 7, 2017

Breast Cancer

Herceptin® (trastuzumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the **treatment of patients with breast cancer** who meet criteria (A) **AND one or more** of the indications listed in (B) below:

C. Individuals whose breast tumors 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/CEP 17 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

D. Individuals meet **one or more** of the following indications:
    1. As a component of neoadjuvant therapy prior to surgical treatment;**or**
    2. As adjuvant treatment of breast cancer to complete a 12-month (52 weeks) course of trastuzumab; **or**
    3. In combination therapy with pertuzumab when the criteria to treat breast cancer in Medical Policy for Pertuzumab (Perjeta®) are met; **or**
    4. In combination therapy with lapatinib as a treatment of metastatic breast cancer when **both** of the following criteria are met:
        a. Individual has received or is receiving trastuzumab-based therapy; **and**
        b. Disease has progressed on or after trastuzumab therapy; **or**
    5. As treatment of metastatic breast cancer, as a single agent or in combination with chemotherapy (any chemotherapy approved for use in breast cancer, except when the combination is addressed in another medically necessary or investigational and not medically necessary statement below) either in treatment-naive individuals or individuals already receiving chemotherapy.

Gastric, Esophageal and Gastroesophageal Adenocarcinoma

Herceptin®(trastuzumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for individuals with **locally advanced or metastatic gastric, esophageal or gastroesophageal (GE) junction adenocarcinoma** who meet criteria: (A) **AND** in addition, **BOTH** of the criteria listed in (B) below:

C. Individuals whose tumors have HER2 protein overexpression documented by **one** of the following:
    1. Immunohistochemistry (IHC) 3+; **or**
    2. Fluorescent in situ hybridization (FISH) HER2 gene copy is greater than 6; **or**
    3. FISH ratio of HER2 gene/chromosome 17 ratio is greater than or equal to 2.0;

AND

D. Individuals meet the following criteria:
    1. Used in combination treatment; **and**
    2. Trastuzumab is used in only one line of therapy.

Except as noted above, **Herceptin® (trastuzumab) does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for the treatment of all other conditions including**,** but not limited to**,** HER2-negative breast cancer, and the following cancers which may be HER2-positive: osteosarcoma, non-small-cell lung, ovarian, prostate, head and neck, esophageal (except as noted above), gastric (except as noted above), pancreatic, colorectal, endometrial, or urothelial.

Blue Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate 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:

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 two pivotal clinical trials. In one trial, single-agent trastuzumab was given to women (n=222) who had received one or two courses of cytotoxic chemotherapy, yielding an objective response rate (ORR) of 15% and a median duration of response of 9.1 months. 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). 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 alone, the FDA and others subsequently cautioned against using a regimen that combined trastuzumab with doxorubicin.

Similar efficacy results have been subsequently reported with the combination of trastuzumab with docetaxel (D) in 188 patients with metastatic breast cancer. 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%. 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.

Kaufman et al reported the results of the first randomized phase III trial combining a hormonal agent (aromatase inhibitor anastrozole) and trastuzumab without chemotherapy. 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 ration [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 et al investigated whether trastuzumab should be given beyond disease progression in women with HER2-positive locally-advanced or metastatic breast cancer. 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).

In 2011, von Minckwitz et al reported on the final analysis of OS from this study. After a median follow-up of 20.7 months, only 32 patients out of 151 were living and 119 (78.8%) had died. No significant differences between treatment arms were found in median OS (20.6 months in the capecitabine groups vs. 24.9 in the combination group; HR: 0.94 [95% CI: 0.65-1.35]; p=0.734). Nor was there a significant difference in OS between treatment arms in patients who had a clinical response or clinical benefit. However, the authors reported a post-hoc analysis demonstrated a survival benefit with post-progression third-line chemotherapy with trastuzumab. In the 52 patients who received third-line chemotherapy with trastuzumab, post-progression survival was 18.8 months (95% CI: 12.9-24.8) versus 13.3 months (95% CI: 10.2-14.7) in the 88 patients who did not receive trastuzumab with third-line chemotherapy (HR: 0.63; P=0.02).

Balduzzi et al in 2014 included these and other trials in a Cochrane review of trastuzumab-containing regimens for metastatic breast cancer. Overall methodologic quality was considered moderate; all trials were open-label, although this likely did not impact OS results, and two trials

that permitted crossover to trastuzumab at progression did not censor OS results at the time of crossover. Trials varied in chemotherapy regimens and treatment line (ie, first- or subsequent-line in the metastatic setting). Median follow-up was two years. Meta-analyses favored trastuzumab-containing regimens for OS (five trials, total N=1309; pooled HR for death, 0.82 [95% CI, 0.71 to 0.94], p=0.004; $I2$=0%) and for progression-free survival (seven trials, total N=1489; pooled HR for progression or disease-related death, 0.61 [95% CI, 0.54 to 0.70], p<0.001; $I2$=12%). Congestive heart failure (CHF) occurred more commonly with trastuzumab containing regimens (seven trials, total N=1459; pooled relative risk [RR], 3.49 [90% CI, 1.88 to 6.47]; p<0.001; $I2$=0%), although more than half of patients were in a single trial of anthracycline-containing regimens. A 2016 meta-analysis included studies published between January 1995 and March 2014; reviewers selected 13 RCTs (9 adjuvant setting, 4 neoadjuvant setting; n=14,546 patients). Results in the adjuvant setting favored trastuzumab-containing regimens for OS (8 trials; pooled HR for death, 0.79; 95% CI, 0.68 to 0.92; p=0.002; $I2$=62%) and for recurrence (6 trials; pooled HR for recurrence, 0.66; 95% CI, 0.58 to 0.75; p<0.001; $I2$=70%).

Section Summary

Multiple randomized controlled trials (RCTs) have established the efficacy of trastuzumab in combination with paclitaxel as first-line treatment for HER2-overexpressing metastatic breast cancer and as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received 1 or more chemotherapy regimens for metastatic disease. Subsequent publications have confirmed these findings.

Adjuvant

Results from randomized trials conducted in 2005 and 2006 have provide data on clinical outcomes of adjuvant trastuzumab therapy: the Breast Cancer International Research Group 006 trial (BCIRG 006, n=3222); the Herceptin Adjuvant Trial (HERA, n=5090); the North Central Cancer Treatment Group N9831 trial (NCCTG N9831, n=3505); the North American National Surgical Adjuvant Breast and Bowel Project B31 trial (NSABP B-31, n=2030); the Finnish Herceptin Study (FinHer, n=232); and the Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trial. 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. The following table summarizes the design and results of those trials.

Duration of Therapy

Updated results from the HERA trial (see Table 1) indicated that two years of adjuvant trastuzumab was not more effective than one year of treatment but was associated with more adverse events. The PHARE trial (see Table 1) supported one year of trastuzumab rather than six months of treatment.

Table 1. Summary of Trastuzmab Trials for Adjuvant Therapy of Breast Cancer

Trial (Year)	Tumor Characteristics	Design	Trastuzumab Schedule	Median FU, Years
BCIRG (2005)	Node-positive, or high risk node negative	AC→D	Q1wk with chemo	3
		AC→D	Q3wk postchemo	
Slamon (2011)		DCH		
HERA (2005)	Node-postive, or node-negative with tumor ≥1cm	Accepted chemo	Q 3wk postchemo	2
Gianni (2011)		Chemo→H (1y)		4[a]
Goldhirsch (2013)		Chemo→H (2y)		8[a]
NCCTG N9831 (2005), (2011)	Node-positive, or if node-negative, with primary tumor >1cm if ER/PR-negative, or >2cm if ER/PR-positive	AC→P	Q1wk with chemo	2
		AC→PH	Q1wk postchemo	3.9
NSABP B-31 (2005) (2011)	Node-positive	AC→P	Q 1wk with chemo	
		AC→PH	Q1wk postchemo	
FinHer (2006)	Node-positive, or node-negative and ≥2cm and PR-negative	D or V→FEC	Q 1wk x 9wk with chemo	3
Joensuu (2009)		DH or VH→FEC		5
PHARE (2013)	Node-positive or node-negative with tumor ≥ 1cm	Chemo+ H	Q 3wk x 12 or 6 mo with or postchemo	3.5

AC: doxorubicin plus cyclophosphamide; C: carboplatin; chemo: chemotherapy; D: docetaxel; ER/PR: estrogen receptor.progesterone receptor; FEC: 5-fluorouracil plus epirubicin plus cyclophosphamide; NR, not reported; P: paclitaxel; Q: every; V: vinorelbine.
[a] Observation group results included 855 patients (52%) who croseed over to receive trastuzumab.

Table 2 Summary of Traztuzumab Trial Outcomes for Adjuvant Therapy of Breast Cancer

Trial (Year)	DFS HR vs Controls[a]			OS HR vs Controls[a]		
	HR	95% CI	p	HR	95% CI	p
BCIRG (2005)	AC→DH:0.61	0.48 to 0.76	<0.001	AC→DH: 0.59	0.42 to 0.85	0.004
	DCH: 0.67	0.54 to 0.83	<0.001	DCH: 0.66	0.47 to 0.93	0.017
Slamon (2011)	AC→DH: 0.64		<0.001	AC→DH: 0.63		<0.001
	DCH: 0.75		0.04	DCH: 0.77		0.04
HERA (2005)	0.64	0.43 to 0.57	<0.001	0.66	0.47 to 1.23	0.012
Gianni (2011)	0.76	0.66 to 0.87	0.001	0.85	0.70 to 1.04	0.11
Goldhirsch (2013)	0.76	0.67 to 0.86	<0.001	0.76	0.65 to 0.88	<0.001
	2- vs 1-y: 0.99	0.85 to 1.14	0.86	2- vs 1-y: 1.05	086 to 1.28	0.63
NCCTG N9831	Pooled data:	0.39 to 0.59	<0.001	Pooled data:	0.48 to 0.93	0.015

(2005), (2011)	0.48 0.52	0.45 to 0.60	<0.001	0.67	0.50 to 0.75	<0.001
NSABP B-31 (2005) (2011)						
FinHer (2006)	0.42	0.21 to 0.83	0.01	0.41	0.16 to 1.08	0.07
Joensuu (2011)	0.65	0.38 to 1.12	0.12	0.55	0.27 to 1.11	0.094
PHARE (2013)	1.28	1.05 to 1.56	0.29	1.46	1.06 to 2.01	NR[b]

AC: doxorubicin plus cyclophosphamide; C: carboplatin; D: docetaxel; DFS: disease-free survival; NR, not reported; OS: overall survival.
[a] HRs are for the hazard of disease recurrence or disease-related death (for DFS) and for hazard of death (for OS).
[b] Statistical testing indicated that the model used to estimate OS (Cox proportional hazards model) was not applicable.

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.

- Pooled analysis of the NSABP B31, NCCTG N9831, BCIRG, FinHer, and HERA trials showed significant improvement in OS versus controls in patients given adjuvant trastuzumab.
- Only the HERA trial reported that trastuzumab improved DFS in a subgroup with high-risk, node-negative disease, although three other trials included similar patients and found better outcomes in the trastuzumab arm. Few patients were node-negative in NCCTG N9831 and FinHer; in the BCIRG 006, 29% of each arm was node negative. 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.
- Benefits of trastuzumab were independent of estrogen-receptor status or type of previous chemotherapy.
- Results from the two-year trastuzumab arm of the HERA trial showed no significant difference in DFS or OS for patients who received trastuzumab for one or two years. Grade 3 and 4 adverse events were more common in patients who received 2 years of trastuzumab (20%) versus 1 year of trastuzumab (16%).
- Although interim (three-year) results from the FinHer trial suggested that even a short (nine-week) course of trastuzumab may reduce risks of recurrence and death in women with HER2-positive, early stage disease, final (five-year) results did not support this conclusion.
- Pooled analysis of the NSABP B-31 and NCCTG N9831 trials was planned when the required number of events (710) for the definitive statistical ananlysis for the OS was reached. In this analysis (n=4046), published in 2014, median time on study was 8.4 years. Adding trastuzumab to the chemotherapy led to a 37% relative improvement in OS (HR=0.63; 95% Cl, 0.54 to 0.73; p<0.001) and an increase in 10 year OS rate, from

75.2 % to 84%. These results ere accomplished by a 40% improvement in DFS (HR=0.60; 95% Cl, 0.53 to 0.68; p<0.001) and increase in 10-year DFS rate from 62.2% to 73.7%.

- The PHARE trial compared six- and 12-month durations of trastuzumab therapy. Six-month treatment was not found to be non-inferior to 12-month treatment.

Sendur et al in 2014 retrospectively analyzed 271 patients with newly diagnosed HER2-positive breast cancer metastatic to axillary lymph nodes who were treated at two centers in Turkey with trastuzumab for nine weeks (n=155) or 52 weeks (n=116). Overall, groups were similar in demographic characteristics, including comorbid disease, and tumor characteristics. However, in the 52-week group, more patients were younger than 50 years (63% vs 51% in the nine-week group), more patients were pre- or perimenopausal (70% vs 55%), and more patients received adjuvant anthracycline plus a taxane rather than either drug alone or other adjuvant chemotherapy (97% vs 89%). At median follow-up of 43 months in the nine-week group and 26 months in the 52-week group, estimated one-, three-, and five-year DFS did not differ statistically between groups (97%, 85%, 75%, respectively, in the nine-week group vs 94%, 80%, 80%, respectively, in the 52-week group; log-rank test, p=0.76). Similarly, one-, three-, and five-year OS did not differ statistically between groups (99%, 92%, 88%, respectively, in the nine-week group vs 99%, 95%, 78%, respectively, in the 52-week group; log-rank test, p=0.99). Due to baseline imbalances in prognostically relevant factors and differential follow-up, interpretation of these findings is limited. Asymptomatic decline in LVEF occurred in 2% of the nine-week group compared with 16% of the 52-week group; magnitude of LVEF declines were not reported.

In 2015, this same group reported on a retrospective comparison of cardiac adverse events in patients with stage I-III breast cancer treated at the same two institutions in Turkey with adjuvant trastuzumab for nine weeks (n=108) or 52 weeks (n=56). Groups differed in proportion of patients age 50 years or younger (60% in the 52-week group vs 34%), disease stage (stage one: 5% vs 19%; stage III: 48% vs 33%), and adjuvant treatment received (anthracycline plus a taxane: 93% vs 63%; radiotherapy: 89% vs 69%). At median follow-up of 32 months, asymptomatic decline in LVEF (by 15% or more, or by more than 10% to below 50%) occurred in 2% and 30% of patients in the nine-week and 52-week groups, respectively (p<0.001). At a median of 24 months follow-up from the last trastuzumab dose, mean (SD) LVEF was 64% (3%) in both groups (p=0.29).

In the trials listed in Table 2, the incidence of grade III or IV heart failure or cardiac-related death among patients receiving trastuzumab-containing adjuvant regimens ranged from 0% (FinHer) to 4.1% (NSABP B-31) overall, with age and baseline LVEF related to the risk for cardiac dysfunction. Concurrent use of trastuzumab and a taxane following 4 cycles of AC resulted in the highest incidences of heart failure (1.5%, 2.4%, and 3.4% for the BCIRG, N9831, and B-31 trials, respectively). Sequential administration of anthracyclines, taxanes, and trastuzumab resuled in heart failure incidences of 1.4% and 0.5% for the N9831 and HERA trails respectively. The nonanthracycline arm of the BCIRG trial had the lowest incidence of heart failure (0.3%). Although the acceptable incidence of cardiac events overall was likely related to rigorous monitoring during the trials, cross-trial comparsions and conclusions are difficult to

make due to differences in definitions of cardiac events, evaluations for cardiac safety, analyses of cardiac end points (cumulative vs overall incidence), and durations of follow-up.
In 2014, de Azambuja et al reported on cardiac AEs in the HERA trial at median 8 years of follow-up. Incidence of severe CHF, defined as NYHA class III or IV with significant decrease in LVEF, was 0.8% in both 1-year and 2-year trastuzumab grups. Although significant LVEF decrease, defined as decline by 10 percentage points or below 50%, occurred more commonly in the2-year trastuzumab group (7.2% vs 4.1%; p<0.001), more patients in the 2-year group achieved acute recovery, defined as an LVEF of 50% or more at 2 consecutive LVEF assessments (88% of patients in the 2-year group vs 81% of patients in the 1-year group). At approximately 75 months (median) follow-up, 35% of patients who achieved recovery in each group had a subsequent decline in LVEF to less than 50%. Like the 2014 Sendur study, these results suggest that some benefits of trastuzumab on LVEF may be reversible after drug discontinuation.

The long-term evaluation of cardiac toxicity in the N9831 trial was published in 2016 after a median follow-up of 9.2 years. The 6-year cumulative incidence of cardiac events ranged from 2.8% to 3.4% in patients who received paclitaxel then trastuzumab or paclitaxel plus trastuzumab followed by trastuzumab alone compared to 0.6% in patients who received paclitaxel alone.

In a recently published meta-analysis, 5 of 6 adjuvant trastuzumab trials were included. Median follow-up was 8 years. For 2263 patietns with hormone receptor –positive disease, 8-year cumulative incidence of death was 7.8% for the trastuzumab group and 11.6% for the no-trastuzumab group (p<0.005); for 1092 hormone receptor-positive patients with 0 or 1 positive lymph nodes, results were 5.3% and 7.4% (p<0.12), respectively. For 1957 patients with hormone receptor-negative disease, OS results were 12.4% and 21.2% (p<0.001), respectively; for 1040 hormone receptor-negative patients with 0 or 1 positive lymph nodes, results were 8.2% and 12.2% (p=0.084), respectively.

Neoadjuvant
Valachis et al conducted a systematic review and meta-analysis of 515 patients from 5 trials that examined neoadjuvant chemotherapy with trastuzumab for HER2-positive breast cancer. Adding trastuzumab to chemotherapy improved the probability of achieving pathologic complete response (pCR) (relative risk [RR]: 1.85, 95% CI: 1.39-2.46; p<0.001). However, breast-conserving surgery rates were not significantly different with the addition of trastuzumab (odds ratio [OR]: 0.98%, 95% CI: 0.80-1.19, p=0.82).

A 2005 randomized, controlled trial (RCT) examined the benefits of adding trastuzumab to neoadjuvant chemotherapy. 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 three-week cycles) followed by fluorouracil, epirubicin, and cyclophosphamide (FEC; four three-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. 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. At a median follow-up of 36.1 months for randomized patients, no patients in the trastuzumab arm and three patients in the chemotherapy-only arm (one of whom died) experienced recurrence.

Results from RCTs suggest improvements in pCR rates with trastuzumab, although the studies were limited by few disease recurrences or deaths. Analyses from other RCTs and single-arm studies showed that patients with pCR after neoadjuvant chemotherapy (determined postoperatively) had significantly longer OS, DFS, and/or recurrence-free survival than those who did not achieve pCR. This also was true for those who achieved pCR compared with those who achieved clinically complete responses but were subsequently shown by postoperative pathology to have residual (microscopic) invasive disease. Thus, improving the pCR rate by adding trastuzumab to neoadjuvant chemotherapy for *HER2*-positive patients with high-risk, larger tumors predicts improved OS and DFS.

Clinical practice supports use of neoadjuvant trastuzumab for *HER2*-positive patients receiving neoadjuvant chemotherapy, even if the 1 available RCT did not show an increase in the proportion of patients given breast-conserving surgery. When used to reduce the risk of recurrence for patients with operable breast cancer, chemotherapy is usually completed before surgery (neoadjuvant chemotherapy) or not begun until after (adjuvant chemotherapy). Those who complete preoperative chemotherapy rarely receive adjuvant 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 to 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 of adjuvant therapy. Consequently, it seems reasonable to initiate trastuzumab with chemotherapy for *HER2*-positive patients receiving neoadjuvant chemotherapy. In neoadjuvant therapy trials, patients continued trastuzumab after surgery to complete 1 year of treatment (see, eg, Bonnefoi et al [2015] and Gianni et al [2014]). However, in a single-center, retrospective review (N=589), Gonzalez-Angulo et al (2015) showed that, among patients who achieved pCR after 24 weeks of trastuzumab-based neoadjuvant chemotherapy, adjuvant trastuzumab did not impact OS or recurrence-free survival. Prospective trials are needed to confirm this finding.

Unresolved Issues Related to Breast Cancer

RCTs have consistently reported a beneficial effect of adjuvant trastuzumab in combination with adjuvant chemotherapy in patients with completely resected *HER2*-positive breast cancer. However, these trials have not resolved the following issues: starting trastuzumab after adjuvant chemotherapy and concurrent versus sequential therapy using trastuzumab.

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 before the announcement of trial results. This group of patients still has not been formally studied. Patients in the HERA trial started trastuzumab a median of 8 months after diagnosis and 3 months after completing all chemotherapy.

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. Six-year interim results of the NCCTG N9831 trial (see discussion above) demonstrated longer disease-free survival with concurrent (with paclitaxel) trastuzumab than with sequential trastuzumab.

Other HER2 Overexpressing Metastatic Cancers
Gastric Cancer
There is 1 Phase II and 1 Phase III trial have been reported on the use of trastuzumab in advanced gastric cancer. Grávalos et al reported a Phase II, single-arm study of 22 chemotherapy-naïve patients who had advanced gastric or gastroesophageal junction cancer with overexpression/amplification of HER2. Patients received trastuzumab in combination with chemotherapy (cisplatin) every 21 days until disease progression, unacceptable toxicity, or study withdrawal. Twenty-one (95%) of 22 patients were able to be evaluated. Seven patients (33%) responded (1 complete response [CR] and 6 partial responses [PRs]). Median time to progression was 5.1 months (95% CI, 3.3 to 6.9). Median OS was 12.9 months (95% CI, 9.1 to 16.6); six- and 12-month OS were 64% and 55%, respectively. The most common grade 3 adverse events were weakness (27%), neutropenia (18%), anorexia (14%), diarrhea (9%), and abdominal pain (9%).

Bang et al (including Van Cutsem) reported the results of the Phase III Trastuzumab in Gastric Cancer (ToGa) trial, 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. Patients who received the trastuzumab were given it every three weeks for six cycles, until disease progression. The primary endpoint of the study was overall survival (OS); 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% were positive. Five hundred ninety-four patients were randomized to the two treatment arms. Median OS for the group that received trastuzumab compared to those that did not was 13.8 months (95% CI: 12 to16 months) versus 11.1 months (95% CI: 10 to 13 months) (HR: 0.74; 95% CI 0.60 to 0.91; p=0.005). ORR was 47% for those who received trastuzumab versus 35% for those that did not (p=0.002). Rates of overall grade 3 or 4 adverse events (68% in both groups) and cardiac adverse events (6% in

both groups) 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 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 seven of 100 patients screened had 2+ or 3+ HER2 expression by immunohistochemistry, as required for study eligibility. Another study reported treatment with trastuzumab as a single agent demonstrated poor efficacy in 18 patients with advanced hormone-refractory prostate cancer.

Salivary Gland Cancer
A 2003 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 over express HER2.

Ovarian and Peritoneal Cancer
A 2003 study of trastuzumab in patients with recurrent or refractory ovarian or primary peritoneal carcinoma found a low rate of clinical response to treatment.

Non-small Cell Lung Cancer
Three Phase II trials in 2004examined trastuzumab plus chemotherapy to treat non-small cell lung cancer. Each of these studies reported that the addition of trastuzumab did not improve outcomes.

In 2005, 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
Oudard et al (2015) in Europe conducted a phase two, open-label, multicenter RCT of trastuzumab in patients with unresectable locally advanced (18%) or metastatic (82%) HER2-positive urothelial carcinoma. HER2-positivity was defined as 2+ or 3+ on IHC confirmed by positive FISH. Of 563 patients screened, 61 were HER2-positive and met eligibility criteria. Most patients (89%) had urothelial carcinoma of the bladder, 5% had carcinoma of the renal pelvis, and 7% had carcinoma of the ureter. However, due to low enrollment, the trial was discontinued. Enrolled patients were randomized 1:1 to receive gemcitabine plus platinum chemotherapy with (n=32) or without (n=29) trastuzumab. Median duration of trastuzumab therapy was ten months (range, 1-27); median number of chemotherapy cycles was eight in the trastuzumab group and six in the chemotherapy-only group. There were no statistical differences

in median PFS (the primary outcome; 8.2 [95% CI, 4.6 to 10.6] with trastuzumab vs 10.2 months [95% CI, 4.3 to 13.4] chemotherapy; log-rank test, p=0.69), ORR (53% with trastuzumab vs 66% chemotherapy; p=0.39), or median OS (14.1 months [95% CI, 9.3 to 28.0] with trastuzumab vs 15.7 [95% CI, 12.2 to 23.6] chemotherapy; log-rank test, p=0.684). Incidence of AEs was similar between groups.

In 2005 and 2006, 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). 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 five 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.

Pancreatic Cancer

A 2012 Phase II study to evaluate trastuzumab and capecitabine for first-line treatment of pancreatic cancer was closed early due to low identification of patients with HER2 overexpression and slow recruitment. Only 23 patients out of 212 patients screened were identified as having HER2 overexpression. Of these 23 patients, 17 were treated with trastuzumab and capecitabine. At 12 weeks of treatment, 13 patients had disease progression, and the PFS was estimated to be 23.5% (95% CI: 6.8% to 49.9%). In this small sample, the addition of trastuzumab to treatment with capecitabine did not improve survival outcomes for pancreatic cancer. In another Phase 1/2 single-arm, nonrandomized trial in patients with advanced pancreatic cancer who failed first-line gemcitabine chemotherapy, objective responses were not observed in any patients.

Osteosarcoma

The safety and feasibility of trastuzumab in combination with standard chemotherapy was tested in a non-randomized, Phase II single-arm study of patients with metastatic osteosarcoma and HER2 overexpression. Forty-one of 96 evaluable patients with newly diagnosed metastatic osteosarcoma had tumors that were HER2-positive by immunohistochemistry; 55 were HER2-negative. All patients received cytotoxic chemotherapy comprising cisplatin, doxorubicin, methotrexate, ifosfamide, and etoposide. Patients with HER2 overexpression received concurrent therapy with trastuzumab given for 34 consecutive weeks; patients with HER2-negative disease received only chemotherapy. The 30-month event-free survival (EFS) and OS rates for patients with HER2 overexpression treated with chemotherapy and trastuzumab were 32% and 59%, respectively. Among patients with HER2-negative disease, treated with chemotherapy alone, the 30-month EFS and OS rates were 32% (p=0.54) and 50% (p=0.58), respectively, compared to those who received combined treatment. There was no clinically significant short-term cardiotoxicity in patients treated with trastuzumab and doxorubicin, although dexrazoxane was administered to reduce the risk of such cardiotoxicity.

Summary

For individuals who have human epidermal growth factor receptor 2 (HER2) overexpressing breast cancer who receive trastuzumab as adjuvant, neoadjuvant, or treatment of metastatic disease, the evidence includes randomized controlled trials (RCTs), single-arm trials, and a

meta-analysis. Relevant outcomes are overall survival, disease-specific survival, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Trastuzumab has shown a survival benefit for primary and metastatic breast cancer patients and has become the accepted and usual therapy for patients with *HER2*-positive breast cancer. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who receive trastuzumab plus cisplatin and capecitabine or 5-fluorouracil, the evidence includes a RCT and a single-arm trial. Relevant outcomes are overall survival, disease-specific survival, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. Trastuzumab has shown a survival benefit for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in 1 Phase 3 trial that reported a 2-month overall survival benefit in the trastuzumab arm and no difference in severe adverse events between the groups that received chemotherapy plus trastuzumab and chemotherapy alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Key Words:

Breast Cancer, Herceptin, Trastuzumab, Gastric cancer , HER2, human epidermal growth factor receptor, gastroesophageal junction adenocarcinoma

Approve by Governing Bodies

Trastuzumab (Herceptin®; Genentech) is a humanized monoclonal antibody against the extracellular domain of human epidermal growth factor receptor 2 (HER2). Trastuzumab was cleared for marketing by the Food and Drug Administration (FDA) through the biologics license application process for treatment of *HER2*-positive breast cancer, in both the adjuvant and metastatic settings, and metastatic gastric or gastroesophageal junction adenocarcinoma. 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.

Current FDA-approved labeling, as of September 2016, states that trastuzumab is indicated as follows:

1. For adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with 1 high-risk feature) breast cancer.
   - as part of a treatment regimen consisteing of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
   - as part of a treatment regimen with docetaxel and carboplatin; or
   - as a single agent following multimodality anthracycline-based therapy.

   Trastuzumab is administered by intravenous (IV) infusion weekly or every 3 weeks for a total of 52 weeks depending on the dosing schedule and chemotherapy used for adjuvant treatment.

2. For treatment of HER2 overexpressing metastatic breast cancer in combination with paclitaxel for first-line treatment; or as a single agent in patients who have received 1 or one chemotherapy regimens for metastasis disease. Trastuzuman is administered by IV infusion weekly until disease progression.
3. For treatment of HER2 overexpressing metastatic gastric or gastroesphagem junction adenocarcinoma, in combination with cisplatin and capecitabine or 5-fluorouracil, in patients who have not received prior treatment for metastatic disease. Trastuzumab is administered by IV infusion every 3 weeks until disease progression.

Trastuzumab received FDA marketing approval only for breast cancer in specific settings and for gastric or gastroesophageal junction adenocarcinoma. 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.

Benefit Application:

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

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

HCPCS Codes:

J9355 Injection, trastuzumab, 10 mg

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Policy History

Medical Policy Group: policy transferred to pharmacy with effective date September 1, 2015.
Medical Policy Group, February 2017 (2): Updates to Description, Key Points, Key Words, Approved by Governing Bodies and References; Policy statement updated to include clarifying statement for breast cancer criteria and added drugs included with combination therapy for gastric, esophageal and gastroesophageal adenocarcinoma.
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