MEDICAL POLICY

POLICY TITLE	**TRASTUZUMAB (HERCEPTIN ®)**
POLICY NUMBER	**MP-2.104**

Original Issue Date (Created):	**July 1, 2002**
Most Recent Review Date (Revised):	**September 24, 2013**
Effective Date:	**November 1, 2013**

I. POLICY

NOTE: The safety and effectiveness of Herceptin in pediatric patients has not been established.

HER2-positive Breast Cancer

Trastuzumab (Herceptin®) may be considered **medically necessary** for the treatment of patients with breast cancer whose tumors over express the HER2 protein (HER2 positive breast cancer). This includes use as adjuvant therapy, neoadjuvant therapy, and treatment of metastatic disease.

Conditions Other Than HER2-positive Breast Cancer

Trastuzumab may be considered **medically necessary**, when used in combination with systemic chemotherapy, for treatment of patients with advanced (locally advanced or metastatic) gastric cancer or gastroesophageal junction adenocarcinoma whose tumors overexpress the HER2 protein (HER2-positive cancer).

Except as noted in the policy criteria above, trastuzumab 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, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

Policy Guidelines

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 the Rationale section, 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. However, these trials have not resolved the following issues:

Duration of therapy

While data support the use of adjuvant trastuzumab for one year, evidence is inadequate to determine if a second year of trastuzumab therapy increases benefit. This comparison is a focus of the HERA trial (see the Rationale section), 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 (see the Rationale section) 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 (e.g., at 3, 6, and 12 months) without an unacceptable decrease (e.g., 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 nonmetastatic (M0) disease.

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II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids
[N] PPO
[N] HMO
[N] SeniorBlue HMO (see note)
[N] SeniorBlue PPO (see note)
[N] Indemnity
[N] SpecialCare
[N] POS
[Y] FEP PPO*

Note: "Off-label use of FDA approved drugs and biologicals used in an anti-cancer chemotherapeutic regimen for medically accepted indications may be covered under Medicare if the indications are supported in either one or more Medicare recognized compendia or in peer-reviewed literature. Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.5- Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen) for the compendia list." *http://www.cms.gov*.

*Refer to FEP Medical Policy Manual MP-10.03.02 . Herceptin (Trastuzumab) The FEP Medical Policy manual can be found at: http://bluewebportal.bcbs.com/landingpagelevel3/504100?docId=23980

III. DESCRIPTION/BACKGROUND

In certain cancers, the human epidermal growth factor receptor 2 (HER2) gene is amplified and overexpressed. Trastuzumab (Herceptin) is a humanized monoclonal antibody, HER2 protein receptor antagonist, which may be used for the treatment of certain cancers which overexpress HER2.

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 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 overexpress HER2.

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Regulatory Status

Trastuzumab (Herceptin®) 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 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.

The current FDA-approved labeling, as of October 2010, indicates Trastuzumab is indicated as follows:

1. For adjuvant treatment of HER2 over-expressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer:
    - as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, **and** either paclitaxel or docetaxel;
    - as part of a treatment regimen of docetaxel and carboplatin; **or**
    - as a single agent following multi-modality anthracycline-based therapy.

    Trastuzumab is administered by IV infusion weekly or every three 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 one or more chemotherapy regimens for metastatic disease. Trastuzumab is administered by IV infusion weekly until disease progression.

3. For treatment of HER2 overexpressing metastatic gastric or gastroesophageal 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 three weeks until disease progression.

IV. RATIONALE

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. (1) 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). (2) The addition of trastuzumab to chemotherapy resulted in an increased response rate (50% vs. 32%, respectively; p<0.001), longer median response duration (9.1 vs. 6.1 months, respectively; p<0.001), and prolonged overall survival (OS) (25.1 months vs. 20.3, respectively; 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. (3, 4)

Similar efficacy results have been subsequently reported with the combination of trastuzumab with docetaxel (D) in 188 patients with metastatic breast cancer. (5) 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%. [reviewed in (6, 7)] These early studies also have shown that trastuzumab can be combined with nonapproved 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. (8) Patients were postmenopausal with human epidermal growth factor receptor (HER2) and hormone receptor-positive metastatic disease (patients with central nervous system [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. (9) 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 endpoint 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; HR: 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 and colleagues reported on the final analysis of OS from this study. (10) 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).

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) (11); the Herceptin Adjuvant Trial (HERA, n=5,090) (12); the North Central Cancer Treatment Group N9831 trial (NCCTG N9831, n=3,505) (13); the North American National Surgical Adjuvant Breast and Bowel Project B31 trial (NSABP B31, n=2,030) (14); and, the Finnish Herceptin Study (FinHer, n=232). (15) 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. (7, 16-19). 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 (11)	node-positive, or high-risk node-negative	AC→D AC→DH DCH	Q1wk w/CTx Q3wk postCTx	3	AC→DH: 0.61 [0.48-0.76] (<0.0001) DCH: 0.67	AC→DH: 0.59 [0.42-0.85] (0.004) DCH: 0.66

					[0.54-0.83] (0.0003)	[0.47-0.93] (0.017)
(20)				5	AC→DH: 0.64; (<0.001) DCH: 0.75 (0.04)	AC→DH: 0.63; P<0.001 DCH: 0.77 (0.04)
HERA (12)	node-positive, or node-negative with tumor ≥1 cm	Accepted CTx CTx→H (1 yr) CTx→H (2 yrs)	Q3wk postCTx	2	0.64 [0.43-0.57] (<0.0001)	0.66 [0.47-1.23] 0.0115)
(21)				4*	0·76 [0·66–0·87] (p<0·0001)	0·85 [0·70–1·04] (p=0·11)
NCCTG N9831 (13) (22)	node-positive, or if node-negative, with primary tumor >1 cm if ER/PR-negative, or >2 cm if ER/PR-positive	AC→P AC→P→H AC→PH	Q1wk w/CTx Q1wk postCTx	2 3.9	combined data: 0.48 [0.39-0.59]	combined data: 0.67 [0.48-0.93]
NSABP B31 (14, 22)	node-positive	AC→P AC→PH	Q1wk w/CTx Q1wk postCTx	2 3.9	(<0.0001) 0.52 [0.45 to 0.60] (<0.001)	(0.015) 0.61 [0.50 to 0.75] (<0.001)
FinHer	node-positive, or node-negative and ≥2 cm and PR-negative	D or V→FEC	Q1wk w/CTx	3	0.42	0.41

(15)		[0.21-0.83]	[0.16-1.08]
	DH or VH→FEC	(0.01)	(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.

*Observation group results include 885 patients that crossed over to receive trastuzumab.

Despite substantial differences in trial design and patient characteristics, the latest available data from adjuvant trials of trastuzumab demonstrate consistent, clinically significant improvements in disease-free survival (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. In an interim analysis of N9831, at 6-year follow-up, concurrent trastuzumab with paclitaxel increased DFS over sequential trastuzumab (HR: 0.77; 99.9% CI: 0.53 to 1.11; p=0.02). (23) Furthermore, final results for the 2-year trastuzumab regimen arm in HERA are not yet available.

Grade III/IV heart failure 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 (LVEF) 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 heart failure (1.5%, 2.4%, and 3.4% for the BCIRG, N9831, and B31 trials, respectively). Sequential administration of anthracyclines, taxanes, and trastuzumab resulted in heart failure 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 heart failure. 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

Valachis and colleagues conducted a systematic review and meta-analysis of 515 patients from 5 trials that examined neoadjuvant chemotherapy with trastuzumab for HER2-positive breast cancer. (24) 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 randomized, controlled trial (RCT) has been published on the benefits of adding trastuzumab to neoadjuvant chemotherapy. (25) The study sequentially administered 2 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 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. (26) 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. (26) 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 RCT, the 2-fold increase in pCR rate is unlikely to be a chance result. (25, 26) Analyses from RCTs (27-29) and single-arm studies (30-32) 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 OS and DFS.

Additional reasoning supports considering neoadjuvant trastuzumab medically necessary for HER2-positive patients undergoing neoadjuvant chemotherapy, even if the one available RCT 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.

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. (33) 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 complete response [CR], 5 partial responses [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.

Bang and colleagues (including Van Cutsem) 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. (34) Patients who received the trastuzumab were given it every 3 weeks for 6 cycles, until disease progression. The primary endpoint of the study was 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; 22.1% 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 who 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 (35, 36) 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 IHC, as required for study eligibility. (37) Another study reported treatment with trastuzumab as a single agent demonstrated poor efficacy in 18 patients with advanced hormone-refractory prostate cancer. (38)

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. (39)

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. (40)

Non-small cell lung cancer

Three reports were identified from Phase II trials of trastuzumab plus chemotherapy to treat non-small cell lung cancer. (41-43) 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. (44)

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. (45)

Bladder and kidney cancer

Two uncontrolled small series also reported on trastuzumab for metastatic transitional cell cancer of the bladder (n=7) or bladder and renal pelvis (n=6). (46, 47) 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 CRs and 26 PRs. 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. (48)

Pancreas

A 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. (49) 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 % (exact 95% CI: 6.8-49.9). In this small sample, the addition of trastuzumab to treatment with capecitabine did not improve survival outcomes for pancreatic cancer.

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.(50) 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. Dexrazoxane was administered to reduce the risk of cardiotoxicity caused by trastuzumab and doxorubicin. 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.

Ongoing Clinical Trials

A February 2013 search of online site ClinicalTrials.gov identified 19 active, open Phase III trials using trastuzumab therapy versus no trastuzumab in adjuvant, neoadjuvant, and metastatic breast cancer, in combinations containing cytotoxic, endocrine, and targeted therapies.

Two Phase III trials using trastuzumab to treat malignancies other than breast, were identified. A randomized study of radiotherapy, paclitaxel, and carboplatin with versus without trastuzumab in patients with HER2-overexpressing esophageal adenocarcinoma will determine whether trastuzumab increases DFS when used as part of combination therapy. (NCT01196390) Secondary outcomes include pathologic complete response rate and overall survival. Expected enrollment is 480 with an estimated trial completion date of December 2014. Another Phase III study will compare 2 trastuzumab dosing regimens with cisplatin/capecitabine for metastatic gastric or gastro-esophageal junction adenocarcinoma. (NCT01450696) This trial will enroll 400 patients and has a study completion date of June 2020.

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Summary

In certain cancers, the human epidermal growth factor receptor 2 (HER2) gene is amplified and overexpressed. 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.

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 HER2-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 overall survival 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.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) Guidelines

Breast Cancer

The 2013 NCCN guidelines (51) recommend the use of trastuzumab for breast cancer as follows:

Adjuvant therapy:

Hormone receptor positive and HER2 positive disease:

- Nodal micrometastases, tumor ≤0.5 cm or microinvasive → adjuvant endocrine therapy or chemotherapy + trastuzumab followed by endocrine therapy (category 2A)
- Node negative or nodal micrometastases, tumor 0.6-1.0 cm→ adjuvant endocrine therapy +/- chemotherapy + trastuzumab (category 2A)
- Node negative or nodal micrometastases, tumor >1 cm→ adjuvant endocrine therapy + chemotherapy + trastuzumab (category 1)
- Node positive (>2 mm)→ adjuvant endocrine therapy + chemotherapy + trastuzumab (category 1)

Hormone receptor negative and HER2-positive disease:

- Nodal micrometastases, tumor ≤0.5 cm or microinvasive, → consider chemotherapy + trastuzumab (category 2A)
- Node negative or nodal micrometastases, tumor 0.6-1.0 cm, → consider chemotherapy + trastuzumab (category 2A)
- Node negative or nodal micrometastases, tumor >1 cm, → adjuvant chemotherapy + trastuzumab (category 1)
- Node positive→ adjuvant chemotherapy + trastuzumab (category 1)

The NCCN guidelines also recommend that patients with HER2-positive breast tumors incorporate trastuzumab up to 1 year (category 1) as part of postoperative adjuvant treatment.

Metastatic:

Guidelines recommend the use of trastuzumab in HER2-positive stage IV disease in combination with selected chemotherapeutics or as a single agent and in patients with HER2-positive disease which has progressed through first-line trastuzumab-containing regimens.

The guidelines note it is unknown what the optimal duration of trastuzumab should be in patients with long-term disease control. For more detail on the recommendations for timing of trastuzumab (i.e., concurrently or sequentially with other treatment) and for specific trastuzumab containing chemotherapy regimens see website: Available online at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf.

Gastric Cancer

The 2012 NCCN guidelines recommend using trastuzumab in combination with systemic chemotherapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B with other chemotherapy combinations) for the treatment of patients with advanced (metastatic or locally advanced) gastric cancer or gastroesophageal junction adenocarcinoma (included in the esophageal cancer guidelines) that is HER-2-positive as determined by standard methods. (52) This recommendation was based on a Phase III trial. (28)

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

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V. DEFINITIONS

ADJUVANT THERAPY refers to additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

METASTATIC DISEASE is the manifestation of a malignancy as a secondary growth arising from the primary growth in a new location. The malignant cells may spread via direct extension or through the lymphatic circulation, the bloodstream or avenues such as the cerebrospinal fluid.

MONOCLONAL ANTIBODY is an antibody specific to a certain antigen. Monoclonal antibodies are created in the laboratory.

NEOADJUVANT THERAPY refers to treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

OFF-LABEL DRUG USE is the use of a drug to treat a condition for which it has not been approved by the U.S. Food and Drug Administration (FDA), especially when it may relieve unpleasant symptoms or prove compassionate. Drug effects that have been observed but not specifically proven (and for which no application has been made) may be utilized for unproven or "off-label" uses by licensed medical practitioners.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

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IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information.

Covered when medically necessary:

HCPCS Code	Description
J9355	INJECTION, TRASTUZUMAB, 10 MG

ICD-9-CM Diagnosis Code*	Description
151.0	MALIGNANT NEOPLASM OF CARDIA
151.1	MALIGNANT NEOPLASM OF PYLORUS
151.2	MALIGNANT NEOPLASM OF PYLORIC ANTRUM
151.3	MALIGNANT NEOPLASM OF FUNDUS OF STOMACH
151.4	MALIGNANT NEOPLASM OF BODY OF STOMACH
151.5	MALIGNANT NEOPLASM OF LESSER CURVATURE OF STOMACH, UNSPECIFIED
151.6	MALIGNANT NEOPLASM OF GREATER CURVATURE OF STOMACH, UNSPECIFIED
151.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF STOMACH
151.9	MALIGNANT NEOPLASM OF STOMACH, UNSPECIFIED SITE
174.0	MALIGNANT NEOPLASM OF NIPPLE AND AREOLA OF FEMALE BREAST
174.1	MALIGNANT NEOPLASM OF CENTRAL PORTION OF FEMALE BREAST
174.2	MALIGNANT NEOPLASM OF UPPER-INNER QUADRANT OF FEMALE BREAST

174.3	MALIGNANT NEOPLASM OF LOWER-INNER QUADRANT OF FEMALE BREAST
174.4	MALIGNANT NEOPLASM OF UPPER-OUTER QUADRANT OF FEMALE BREAST
174.5	MALIGNANT NEOPLASM OF LOWER-OUTER QUADRANT OF FEMALE BREAST
174.6	MALIGNANT NEOPLASM OF AXILLARY TAIL OF FEMALE BREAST
174.8	MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF FEMALE BREAST
174.9	MALIGNANT NEOPLASM OF BREAST (FEMALE), UNSPECIFIED SITE
175.0-175.9	MALIGNANT NEOPLASM OF NIPPLE AND AREOLA OF MALE BREAST
230.2	CARCINOMA IN SITU OF STOMACH
233.0	CARCINOMA IN SITU OF BREAST
V10.3	PERSONAL HISTORY OF MALIGNANT NEOPLASM OF BREAST
V58.11	ENCOUNTER FOR ANTINEOPLASTIC CHEMOTHERAPY
V58.12	ENCOUNTER FOR ANTINEOPLASTIC IMMUNOTHERAPY

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2014:

ICD-10-CM Diagnosis Code*	Description
C16.0	Malignant neoplasm of cardia
C16.4	Malignant neoplasm of pylorus
C16.3	Malignant neoplasm of pyloric antrum
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast

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ICD-10-CM Diagnosis Code*	Description
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast

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ICD-10-CM Diagnosis Code*	Description
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
D00.2	Carcinoma in situ of stomach
D05.12	Intraductal carcinoma in situ of left breast
D05.11	Intraductal carcinoma in situ of right breast
D05.10	Intraductal carcinoma in situ of unspecified breast
D05.02	Lobular carcinoma in situ of left breast
D05.01	Lobular carcinoma in situ of right breast
D05.00	Lobular carcinoma in situ of unspecified breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.80	Other specified type of carcinoma in situ of unspecified breast
D05.92	Unspecified type of carcinoma in situ of left breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.90	Unspecified type of carcinoma in situ of unspecified breast
Z85.3	Personal history of malignant neoplasm of breast
Z51.11	Encounter for antineoplastic chemotherapy
Z51.12	Encounter for antineoplastic immunotherapy

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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X. POLICY HISTORY

MP 2.104	**CAC 6/24/03**
	CAC 5/31/05
	CAC 1/31/06
	CAC 2/28/06
	CAC 2/27/07
	CAC 3/25/08
	CAC 11/24/09 Policy statement clarified.
	CAC 9/28/10 Added new medically necessary indications (HER2- positive gastric cancer and gastroesophageal junction adenocarcinoma)
	CAC 10/25/11 Consensus. BCBSA match
	CAC 6/26/12 Minor revision. FEP variation revised. Background information revised to list the most current FDA-approved indications.
	7/28/13 Admin coding review complete--rsb
	CAC 9/24/13 consensus review. No change to policy statements. References updated. Rationale section added.

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