Description

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 that 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/epidermal growth factor receptor [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 have 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 may also 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 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.

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 overexpressing 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 [intravenous] 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 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 3 weeks until disease progression.

**Policy**

**HER2-positive Breast Cancer**

Trastuzumab may be considered *medically necessary* for the treatment of patients with breast cancer whose tumors overexpress 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).

Trastuzumab 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, and urothelial.

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.

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 capcitabine, 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.

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Tumor Characteristics</th>
<th>Design</th>
<th>Trastuzumab Schedule</th>
<th>F/U (median, years)</th>
<th>DFS HR vs. Controls [95% CI] (p)</th>
<th>OS HR vs. Controls [95% CI] (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG (11)</td>
<td>node-positive, or high-risk node-negative</td>
<td>AC→D</td>
<td>Q1wk w/CTx</td>
<td>3</td>
<td>AC→DH: 0.61 [0.48-0.76] (&lt;0.0001)</td>
<td>AC→DH: 0.59 [0.42-0.85] (0.004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC→DH</td>
<td>Q3wk postCTx</td>
<td></td>
<td>DCH: 0.67 [0.54-0.83] (0.0003)</td>
<td>DCH: 0.66 [0.47-0.93] (0.017)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCH</td>
<td></td>
<td>5</td>
<td>AC→DH: 0.64; 0.63; P&lt;0.001 (&lt;0.001)</td>
<td>DCH: 0.77</td>
</tr>
</tbody>
</table>
HERA
(12)

node-positive, or
node-negative with

tumor ≥1 cm

Accepted
CTx

CTx→H (1 yr)

CTx→H

(2 yrs)

Q3wk
postCTx

2

0.75 (0.04)

0.64 [0.43-

0.57]

(0.0001)

0.66 [0.47-

1.23] 0.0115

(0.04)

2

0.76 [0.66-

0.87]

(0.0001)

(0.0001)

(0.0001)

4*

(0.0001)

combined

data:

combined
data:

0.48

0.67

[0.39-0.59]

[0.48-0.93]

(0.0001)

(0.015)

2

NSABP
B31 (14,
node-positive
22)

node-positive, or

node-negative and

≥2 cm and PR-

negative

or ≥2 cm

if ER/PR-negative, or >2 cm

if ER/PR-positive

AC→P

AC→P→H

AC→PH

Q1wk w/CTx

Q1wk

postCTx

Q1wk

postCTx

AC→P

AC→PH

Q1wk w/CTx

Q1wk

postCTx

D or

V→FEC DH

or

VH→FEC

Q1wk w/CTx

0.52

0.61

[0.45 to 0.60]

[0.50 to 0.75]

(0.0001)

(0.0001)

3.9

3.9

2

FinHer
(15)

node-positive, or

node-negative, with

primary tumor >1

cm if ER/PR-

negative, or >2 cm

if ER/PR-positive

D or

V→FEC DH

or

VH→FEC

Q1wk w/CTx

0.42 [0.21-

0.83] (0.01)

0.41 [0.16-

1.08] (0.07)

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

*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

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FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of FirstHealth
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.

Ongoing Clinical Trials

A March 2012 search of online site ClinicalTrials.gov identified 9 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.

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 current 2012 NCCN guidelines (50) 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 +/- chemotherapy + trastuzumab (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:

**Gastric Cancer**

The 2011 NCCN guidelines recommend (category 2A) using trastuzumab in combination with systemic chemotherapy 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. (51) This recommendation was based on a Phase III trial. (28)

As of March 2012, use of trastuzumab has not been addressed by any of the NCCN guidelines for the following malignancies: osteosarcoma, ovarian, prostate, head and neck, pancreatic, colon, rectal, endometrial, urothelial or non-small cell lung cancers.

References:


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<tr>
<td>CPT</td>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug (new code effective 1/1/09 - code number was 90774)</td>
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<tr>
<td>ICD-9 Procedure</td>
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<tr>
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**Type of Service**  Prescription Drugs

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