Clinical Policy Bulletin: Trastuzumab (Herceptin), Ado-Trastuzumab (Kadcyla) and Pertuzumab (Perjeta)

Number: 0313

Policy

I. Aetna considers trastuzumab (Herceptin, Genentech, Inc.) medically necessary for use in members with breast cancer, advanced esophageal adenocarcinomas, gastric adenocarcinomas, gastroesophageal junction adenocarcinomas, or non-small cell lung adenocarcinomas that over-express the HER2 (human epidermal growth factor receptor 2) protein (i.e., level 3+ on an immunohistochemical assay) or where HER2 gene amplification is detected using FISH, a HER2 gene/chromosome 17 ratio greater than 2, or HER2 gene copy number greater than 6 signals/nucleus.

For individuals with breast cancer who are HER2-positive with no distant metastatic disease, up to 1 year of Herceptin is considered medically necessary for adjuvant treatment.

II. Aetna considers trastuzumab, alone or in combination with chemotherapy, experimental and investigational for the treatment of the following types of cancer (not an all-inclusive list) and all other indications because trastuzumab has not been proven to be effective for these indications.

- **Ampullary adenocarcinoma**
- Bladder cancer
- Cancers of unknown primary
- Colon cancer
- Dermal adnexal cancer
- Endometrial cancer
- Hepatobiliary cancers (cholangiocarcinoma and gallbladder cancer)
- **Intra-hepatic bile duct cancer**
- Melanoma
- **Neuroendocrine cervical cancer**
- Osteosarcoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Salivary gland/duct cancer
Vulvar cancer.

III. Aetna considers pertuzumab (Perjeta) medically necessary when used in combination with trastuzumab for recurrent or metastatic HER2-positive breast cancer and for neoadjuvant treatment of HER2-positive breast cancer.

IV. Aetna considers pertuzumab, alone or in combination with chemotherapy, experimental and investigational for the treatment of the following types of cancer (not an all-inclusive list) and all other indications because pertuzumab has not been proven to be effective for these indications.

- Colon cancer
- Gastric cancer
- Hepatobiliary cancers (cholangiocarcinoma and gallbladder cancer)
- Lung cancer (including non-small-cell lung cancer)
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Rectal cancer
- Uterine cancer.

V. Aetna considers ado-trastuzumab emtansine (Kadcyla) medically necessary for the treatment of members with HER2-positive recurrent or metastatic breast cancer who were previously treated with trastuzumab.

VI. Aetna considers ado-trastuzumab emtansine experimental and investigational for all other indications (e.g., colorectal cancer, HER2-negative breast cancer, gastric cancer, hepatobiliary cancers (cholangiocarcinoma and gallbladder cancer)) because its effectiveness for indications other than the one listed above has not been established.

Note: Dosing information is provided as an appendix to the background section.

Background

The HER2 gene normally produces a small amount of protein called HER2 growth factor cell-surface receptor, which is responsible for growth and division of cells. In 25 to 30% of women with breast cancer, there is a genetic alteration in the HER2 gene that results in increased amounts of this protein, and this protein over-expression is associated with more aggressive disease and shortened survival because it may be resistant to chemotherapy and other forms of treatment.

The HercepTest, manufactured by Dako, is a commercially available test that specifically identifies over-expression of HER2/neu (c-erbB-2) protein in patients with breast cancer, and has been approved by the Food and Drug Administration (FDA) for selecting patients for treatment with trastuzumab. It is an immunohistochemical antibody assay designed for the detection of HER2 over-expression of HER2/neu protein using specific antibodies, and localizes over-expressed protein in cells or tissues. HER2 expression has been broken down into 4 levels: 0, 1, 2, 3. HER2/neu over-expression is defined as 2 or 3 circumferential membranous staining with an anti-HER2 antibody by immunohistochemistry (IHC) performed on a paraffin embedded tissue. Clinical trastuzumab trials showed that patients with level 0 to 1 HER2 expression do not benefit from the drug; a few patients with level 2 expression do benefit from the drug; and many patients with level 3 expression also benefit. The
trastuzumab monoclonal antibody seeks out and binds to the specific HER2 or HER2/neu
receptors on the surface of HER2 over-expressing breast cancer cells and directly inhibits
tumor cell growth.

Trastuzumab is indicated for treatment of individuals with HER2 over-expressing breast
cancer both as first line therapy in combination with paclitaxel (Taxol), and as a single agent
in second and third line therapy. Patients are given trastuzumab intravenously once a week.
The appropriate duration of therapy is unknown, although studies have reported patients that
have been treated with trastuzumab for 9 weeks.

In a large, randomized controlled trial, trastuzumab improved response rates to
chemotherapy by 53 % in women with metastatic breast cancer that over-expressed HER2.
In this clinical trial, overall response rates were 43 % with trastuzumab and chemotherapy,
compared to only 28 % in women treated with chemotherapy alone. The greatest
improvement in response rates was seen in patients who received trastuzumab plus the
chemotherapeutic agent paclitaxel. Thirty six percent of women treated with trastuzumab
plus paclitaxel had a tumor response, compared to only 15 % of women receiving paclitaxel
alone. Median duration of response, which is measured from the time the cancer responds to
therapy to the time the cancer begins to spread or grow again, was 7 months longer in
women treated with trastuzumab and paclitaxel than it was in women treated with paclitaxel
alone.

Trastuzumab can also induce responses in patients with HER2 over-expressing metastatic
breast cancers who have failed to respond to chemotherapy. In a trial of 222 women who
had failed 1 or 2 prior chemotherapy regimens, 14 % of women treated with trastuzumab
alone had objective tumor responses with tumor shrinkage of 50 % or more.

Two large randomized controlled clinical trials sponsored by the National Cancer Institute
involving more than 3,300 patients with early-stage HER2 positive invasive breast cancer
found that those patients who received trastuzumab in combination with standard
chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) had a statistically
significant 52 % decrease in risk for breast cancer recurrence compared with patients who
received chemotherapy alone (Romond et al, 2005). These studies included women with
HER2-positive and node-positive breast cancer with no distant metastatic disease. One
study also included persons with high-risk node-negative breast cancer: tumor greater than 2
cm, estrogen/progesterin receptor negative, nuclear grade 2 to 3 or age less than 35 years.
In one study, Herceptin therapy was administered weekly for 3 months, then every 21 days
for 1 year. In another study, Herceptin therapy was administered weekly for 1 year. Four
years into the study, 85 % of women with early-stage HER-2 positive breast cancer who
received trastuzumab were free of recurrence, compared with 67 % of women who did not
receive the drug. The data monitoring committees overseeing the combined analysis of
these trials recommended that the results of a combined interim analysis be made public
because the studies had met their primary endpoints of increasing disease-free survival
(DFS) and overall survival (OS) in patients receiving trastuzumab in combination with
chemotherapy. Most patients in these studies had lymph node-positive breast cancer, with
only a minority having lymph node-negative disease. The limited information in the node-
negative group did not allow for a separate analysis of this group. In these studies, the
likelihood of congestive heart failure in women receiving standard combination chemotherapy
and trastuzumab was increased by 3 % to 4 %.

An international, multi-center, randomized controlled clinical trial (Herceptin Adjuvant Trial
(HERA)) found that 1 year treatment with trastuzumab after adjuvant chemotherapy
significantly improved DFS among women with early stage HER2-positive breast cancer
(Piccart-Gebhart et al, 2005). The study compared 1 or 2 years of trastuzumab given every 3
weeks with observation in women with HER2-positive and either node-negative or node-
positive breast cancer who had completed locoregional therapy (surgery with or without
radiotherapy) and at least 4 cycles of neoadjuvant or adjuvant chemotherapy. Eligible subjects had node-positive disease (regardless of tumor size) or node-negative disease (if tumor size was greater than 1 cm) and no distant metastases. Subjects in the HERA study were assigned to 3 groups: (i) 2 years of treatment with trastuzumab, (ii) 1 year of trastuzumab, and (iii) observation. The study by Piccart-Gebhart reported results only of the groups assigned to 1 year of trastuzumab treatment and observation. At the first planned interim analysis (median follow-up of 1 year), 347 events (recurrence of breast cancer, contralateral breast cancer, second non-breast malignant disease, or death) were observed; 127 events in the trastuzumab group and 220 in the observation group. The unadjusted hazard ratio (HR) for an event in the trastuzumab group, as compared with the observation group, was 0.54 (95% confidence interval [CI]: 0.43 to 0.67), representing an absolute benefit in terms of DFS at 2 years of 8.4%. Overall survival in the 2 groups was not statistically significantly different (29 deaths with trastuzumab versus 37 with observation). Severe cardiotoxicity developed in 0.5% of the women who were treated with trastuzumab.

Fluorescent in situ hybridization (FISH) assays have also been validated for use in the selection of candidates for trastuzumab therapy. FISH assays contain a direct label DNA probe designed to bind to the HER2 gene, allowing direct visualization of the gene. Two FISH kits for HER2 are now available: PathVysion from Visis; and Inform, developed by Oncor and now marketed by Ventana. Tumors that are candidates for trastuzumab therapy can be detected at the DNA level by FISH assays because there is a high correlation between over-expression of the HER2 protein and amplification of the gene that codes for it. Both the PathVysion and Inform FISH tests have been approved by the FDA for quantifying HER2/neu amplification. However, only the PathVysion FISH test has been approved by the FDA for selecting patients with metastatic breast cancer for trastuzumab therapy. FISH assays of HER2 gene amplification have been found to have a high correlation with immunochemical antibody assays for HER2 over-expression. The American Society of Clinical Oncology (ASCO) recommends using either immunohistochemical antibody assays or FISH assays for selecting patients for trastuzumab therapy. ASCO's clinical practice guidelines for the use of tumor markers in breast and colorectal cancer (2001) states that, "[h]igh levels of c-erbB-2 [HER2/neu] expression or c-erbB-2 [HER2/neu] amplification can be used to identify patients for whom trastuzumab expression on a new or stored specimen of tumor tissue. This assay may be of benefit for the treatment of metastatic, recurrent, or treatment-refractory locally advanced breast cancer."

The HER2/neu is over-expressed/amplified in a range of other tumor types including ovarian, bladder, pancreatic, salivary gland, endometrial and non-small-cell lung cancer (Scholl et al, 2001). HER2 is implicated in disease initiation and progression, associated with poor prognosis, and may also predict the response to chemotherapy and hormonal therapy. The prevalence of HER2 over-expression/amplification in various tumor types raises the possibility of using trastuzumab to antagonize the abnormal function of over-expressed HER2 receptors in HER2-positive tumors other than breast. Clinical trials are either planned or underway to assess the therapeutic role of trastuzumab in non-small cell lung cancer, bladder and ovarian cancer.

HER2/neu gene amplification is uncommon in bladder cancer. Evidence from breast cancer suggests that only tumors with HER2/neu gene amplification respond to trastuzumab. If this were true for bladder cancer, only approximately 5% of muscle-invasive transitional cell carcinomas of the bladder would be suitable for treatment (Latif et al, 2004; Kruger et al, 2002). Latif et al concluded that "[t]he role of trastuzumab in these tumours remains untested at present."

HER2/neu gene amplification has also been rarely found in non-small cell lung cancer (Zinner et al, 2004), and clinical studies to date have failed show a demonstrable advantage of trastuzumab in the majority of non-small cell lung cancer patients (Hirsch and and Langer, 2004; Zinner et al, 2004). Langer et al (2004), reporting on the results of the Eastern
Cooperative Oncology Group Phase II study of trastuzumab in non-small cell lung cancer, concluded that overall survival in patients treated with trastuzumab, carboplatin and paclitaxel is similar to historical data using carboplatin and paclitaxel alone. The investigators reported, however, that patients with 3+ HER2/neu expression did well in contrast to historical data suggesting potential benefit for trastuzumab in this rare subset of non-small cell lung cancer. This finding needs to be confirmed by prospective clinical studies with internal controls.

In a multi-center, phase II clinical study, Clamon and colleagues (2005) determined whether trastuzumab would effect responses in patients with non-small cell lung carcinoma who had tumors that over-expressed HER2. Patients were required to have Stage IIIB or Stage IV non-small cell lung carcinoma and tumors with 2+ or 3+ expression of HER2, as determined with immunohistochemistry, and they may have received up to 1 prior chemotherapy regimen. Trastuzumab at a dose of 4 mg/kg was given intravenously on week 1; then, weekly doses of 2 mg/kg were given. Response revaluation was performed every 8 weeks. Among 209 screened patients, 24 patients (11 %) had tumors with 2+ or 3+ expression of HER2. One patient achieved a partial response, and 1 patient experienced a treatment-related death due to pulmonary toxicity. These investigators concluded that single-agent trastuzumab did not exhibit significant clinical activity against non-small cell lung carcinoma when HER2 expression levels were measured by immunohistochemistry.

In a randomized controlled phase II clinical trial, Krug et al (2005) examined whether combined trastuzumab with weekly taxanes would improve outcomes over standard chemotherapy in patients with advanced non-small cell lung cancer. The primary goal was to determine whether docetaxel plus trastuzumab or paclitaxel plus trastuzumab was the superior regimen based on response and toxicity, and to determine whether either regimen was appropriate for further testing in a randomized phase III clinical trial. After stratification based on the results of HER2 immunohistochemistry, chemotherapy-naive patients were randomized to receive trastuzumab plus docetaxel or trastuzumab plus paclitaxel. The study was designed so patients with or without HER2 over-expression would be distributed equally between the study arms. Immunohistochemistry for HER2 protein expression was attempted for 182 pathologic samples from 169 patients. Twenty-eight of the 179 evaluable samples (16 %) revealed 2+ or 3+ staining. The objective response rate was 23 % (7 of 30 patients) in the patients treated with docetaxel plus trastuzumab and 32 % (11 of 34 patients) in the patients treated with paclitaxel plus trastuzumab (p = 0.76). No difference was noted in the median survival (16 months versus 14 months) or 1-year survival (57 % versus 55 %) (p = 0.998). Toxicities were mild in both treatment arms. No difference with regard to response rates or survival was noted between HER2-positive (2+ or 3+) and HER2-negative (0-1+) patients. These authors concluded that the expression of HER-2 protein in patients with advanced non-small cell lung cancer in this study was found to be similar to that reported in previous series. The response rates and toxicities for patients treated with docetaxel and trastuzumab or paclitaxel and trastuzumab were not significantly different, though survival in both arms was better than expected. HER2 expression status did not appear to affect outcomes for this uniform group of patients who were treated in a comparable fashion.

Because of the infrequency of HER2 over-expression, and the absence of improved outcomes in patients with non-small cell lung cancer who were treated with trastuzumab plus chemotherapy in other studies, neither regimen tested will be advanced to a Phase III clinical trial.

The value of trastuzumab in ovarian carcinoma is limited by the low frequency of HER2/neu over-expression and the low response rate of response to trastuzumab among patients with HER2/neu over-expression. Bookman et al (2003) reported on the results of a Gynecology Oncology Group Phase II study of trastuzumab in patients with persistent or recurrent epithelial ovarian or primary peritoneal carcinoma with 2+/3+ HER2 expression. Only 11.4 percent of subjects screened for HER2 expression exhibited the requisite 2+ or 3+ HER2 expression level to be eligible for this study. The investigators reported an overall response
rate of 7.3% after a median treatment duration of 8 weeks, and the median progression-free interval was 2 months. The investigators concluded that “the clinical value of single-agent trastuzumab in recurrent ovarian cancer is limited by the low frequency of HER2 overexpression and low rate of objective response among patients with HER2 over-expression.”

Iwamoto et al (2003) found HER2/neu over-expression in only 1 of 15 clear cell ovarian carcinoma cases that were immunostained for HER-2/neu using HercepTest. The investigators concluded that HER-2/neu over-expression appeared to be uncommon in ovarian clear cell carcinomas. “Herceptin may thus target only a small proportion of ovarian clear cell carcinomas and be of limited clinical value for treatment of this carcinoma” (Iwamoto et al, 2003).

Viani and colleagues (2007) performed a meta-analysis of completed clinical trials of adjuvant trastuzumab in the adjuvant setting. Survival, recurrence, brain metastases, cardiotoxicity and directions for future research were discussed. Relevant reports were reviewed by two reviewers independently and the references from these reports were searched for additional trials, using guidelines set by QUOROM statement criteria. Pooled results from that 5 randomized trials of adjuvant trastuzumab showed a significant reduction of mortality (p < 0.00001), recurrence (p < 0.00001), metastases rates (p < 0.00001) and second tumors other than breast cancer (p = 0.007) as compared to no adjuvant trastuzumab patients. There were more grade III or IV cardiac toxicity after trastuzumab (203/4,555 = 4.5 %) versus no trastuzumab (86/4,562 = 1.8 %). The likelihood of cardiac toxicity was 2.45-fold higher (95 % CI: 1.89 to 3.16) in trastuzumab arms, however that result was associated with heterogeneity. The likelihood of brain metastases was 1.82-fold higher (95 % CI: 1.16 to 2.85) in patients who received trastuzumab. The authors concluded that the findings from this meta-analysis are sufficiently compelling to consider 1 year of adjuvant trastuzumab treatment for women with HER2-positive early breast cancer based on the risk: benefit ratio demonstrated in these studies.

In January 2008, the FDA rendered trastuzumab the additional indication of adjuvant monotherapy for early-stage HER2-positive breast cancer. The FDA decision was predicated on 1-year data from the HERA (HERceptin Adjuvant) trial. It found a significant 46 % reduction in recurrence among women who took trastuzumab for 52 weeks following multi-modality anthracycline-based therapy compared with controls. The HERA trial also reported a significant increase in disease-free survival among women who received adjuvant therapy with trastuzumab. Trastuzumab was, however, associated with a higher rate of congestive heart failure -- 2 % versus 0.3 % in the control group. Serious infusion reactions including fatal infusion reactions as well as pulmonary toxicity have been reported with trastuzumab. In most cases symptoms occurred during infusion or within 24 hours of infusion. Trastuzumab infusion should be interrupted for patients with dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Trastuzumab should be discontinued for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Advanced gastric cancer is an incurable disease; several authorities have stated that new and less toxic treatments are needed. HER2 over-expression has been reported in 6 % to 35 % of stomach and gastroesophageal tumors. Gravalos and Jimeno (2008) noted that gastric cancer is the second leading cause of cancer mortality in the world and its management, especially in advanced stages, has evolved relatively little. In particular, no targeted modality has so far been incorporated to its treatment armamentarium. HER2 over-expression is increasingly recognized as a frequent molecular abnormality, driven as in breast cancer by gene amplification. There is mounting evidence of the role of HER2 over-expression in patients with gastric cancer, and it has been solidly correlated to poor outcomes and a more aggressive disease. Additionally, pre-clinical data are showing significant anti-tumor efficacy of anti-HER2 therapies (particularly monoclonal antibodies directed towards the protein) in vitro as well as in-vivo models of gastric cancer. As a result, several clinical trials are
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exploring in different settings and with diverse designs the potential of anti-HER2 therapies in gastric cancer patients.

A randomized trial investigating anti-HER2 therapy in advanced gastric cancer showed that trastuzumab plus chemotherapy was superior to chemotherapy alone (van Custem et al, 2009). The ToGA study is the first randomized, prospective, multi-center, phase III trial to study the efficacy and safety of trastuzumab in HER2-positive gastric cancer. Patients with HER2-positive gastro-esophageal and gastric adenocarcinoma (locally advanced, recurrent, or metastatic) were randomized to receive trastuzumab plus chemotherapy (5-fluorouracil or capecitabine and cisplatin) every 3 weeks for 6 cycles or chemotherapy alone. Trastuzumab was given until disease progression. The primary end point was OS; secondary end points included overall response rate (ORR), progression-free survival, time to progression, duration of response, and safety. An interim analysis was planned at 75 % of deaths and the Independent Data Monitoring Committee recommended releasing the data as the pre-specified boundary was exceeded and median follow-up of patients was 17.1 months. Tumors from 3,807 patients were centrally tested for HER2 status: 22.1 % were HER2-positive; 594 patients were randomized 1:1 at sites in Europe, Latin America, and Asia. The investigators reported that baseline characteristics were well-balanced across arms. Median OS was significantly improved with trastuzumab plus chemotherapy compared to chemotherapy alone: 13.5 versus 11.1 months, respectively (p = 0.0048; HR 0.74; 95 % CI: 0.60 to 0.91). ORR was 47.3 % in the trastuzumab plus chemotherapy arm and 34.5 % in the chemotherapy arm (p = 0.0017). Safety profiles were similar with no unexpected adverse events in the trastuzumab plus chemotherapy arm. There was no difference in symptomatic congestive heart failure between arms. Asymptomatic left ventricular ejection fraction decreases were reported in 4.6 % of patients in the trastuzumab plus chemotherapy arm and 1.1 % in the chemotherapy arm. The investigators concluded that this randomized trial investigating anti-HER2 therapy in advanced gastric cancer showed that herceptin plus chemotherapy is superior to chemotherapy alone.

National Comprehensive Cancer Network guidelines (NCCN, 2010) recommend the use of herceptin in combination with systemic chemotherapy for persons with advanced, HER2-positive esophageal or gastro-esophageal adenocarcinoma. Homs and colleagues (2009) evaluated current treatment strategies and new developments including targeted therapy for esophageal cancer. Published clinical trials as well as abstracts were selected regarding chemo-radiation or targeted therapy for esophageal cancer. Pre-operative chemotherapy may offer a survival advantage compared to surgery alone, but the evidence is inconclusive. For pre-operative chemo-radiation, only 2 of 10 randomized trials showed advanced survival compared to surgery alone, and, therefore, more phase III trials and, consequently, meta-analyses are needed. Until now, for palliative chemotherapy, no survival benefit has been shown. This is largely due to a lack of studies and difficulties in performing randomized trials. The application of targeted therapy is widespread and reported for several tumor types. For esophageal cancer, most studies have been performed with epidermal growth factor receptor (EGFR) inhibitors, including cetuximab, gefitinib, erlotinib and trastuzumab. Limited experience is available with angiogenesis inhibitors, apoptosis inhibitors and COX-2 inhibitors. As yet, targeted therapies are proven to be safe often in combination with chemo-radiation, but modestly effective for esophageal cancer. Phase III trials have not been published yet and, therefore, for targeted therapies also, possibly using new concepts, more studies are needed.

In a review on systemic therapies for recurrent and/or metastatic salivary gland cancers, Vattemi and colleagues (2008) noted that salivary gland carcinomas are rare cancers, comprising 1 to 5 % of head and neck cancers. They represent a morphologically and clinically diverse group of tumors. The most commonly histopathological types are muco-epidermoid cancer, adenoid cystic cancer and adenocarcinomas. Malignant salivary gland tumors generally present as painless, slow-growing tumors that are indistinguishable from
benign tumors. Surgery is the principal treatment and is curative in early stage. Radiation therapy should be considered in most patients after surgical resection. Chemotherapy is reserved for palliative treatment of metastatic disease but results are disappointing. Recent studies have investigated the role of targeted therapies in a palliative setting. Multi-center cooperative group clinical trials are required to assess novel therapies to maximize patient resources in this uncommon tumor.

Fleming et al (2010) evaluated the effectiveness of single-agent trastuzumab against advanced or recurrent HER2-positive endometrial carcinoma (EC), and explored predictors for HER2 amplification. Eligible patients had measurable stage III, IV, or recurrent EC. There was no limit on prior therapy although total prior doxorubicin dose was limited to 320 mg/m(2). Tumors were required to have HER2 over-expression (2+ or 3+ immunohistochemical staining) or HER2 amplification (FISH HER2/CEP 17 ratio greater than 2.0). Trastuzumab was administered intravenously at a dose of 4 mg/kg in week 1, then 2 mg/kg weekly until disease progression. The primary end point was tumor response. Of the 286 tumors centrally screened by LabCorp, 33 (11.5 %) were HER2-amplified. Three of 8 clear (38 %) cell carcinomas and 7 of 25 serous carcinomas (28 %) screened exhibited HER2 amplification compared with 7 % (2/29) of endometrioid adenocarcinomas. Over-expression of HER2 was correlated with amplification of HER2 (r = 0.459; p < 0.0001). A total of 34 women were enrolled; 1 was excluded (refused treatment); and 18 had tumors with known HER2 amplification. No major tumor responses were observed. Twelve women experienced stable disease, 18 had increasing disease, and 3 were indeterminate for tumor response. Neither HER2 over-expression nor HER2 amplification appeared to be associated with progression-free survival or OS. The authors concluded that trastuzumab as a single agent did not exhibit activity against endometrial carcinomas with HER2 over-expression or HER2 amplification, although full planned accrual of women with HER2 amplified tumors was not achieved due to slow recruitment. Serous and clear cell endometrial carcinomas appear to be more likely to demonstrate HER2 amplification.

Nash and colleagues (2007) reported the case of a 44-year old man was referred for a right chest nodule of 3-month duration. A "benign" nodule had been excised from this location 8 years prior. On examination, palpable nodes were noted in the right axilla. Radiographical studies were significant only for right axillary lymphadenopathy. Histologically, a nodular dermal proliferation composed of poorly differentiated epithelioid cells in nests and focally forming ducts with pseudopapillary architecture comprised the primary tumor. Features of a clear cell hidradenoma were noted focally. Immunohistochemical (IHC) analysis revealed reactivity for HMW cytokeratins, CK5 and CK7, p53, p63, CEA (focal), androgen receptor, EGFR, estrogen receptor (ER), MUC5AC, and strong/diffuse membranous staining for Her-2/neu. Negative stains included villin, TTF-1, CDX2, S-100 protein, vimentin, gross cystic disease fluid protein 15 (GCDP-15), mammoglobulin, and MUC2. A wide local excision and axillary node dissection was performed. Metastatic tumor involved 9 of 28 nodes. Interphase fluorescence in situ hybridization (FISH) demonstrated chromosomal amplification of the Her-2/neu locus within the tumor and a nodal metastasis. The patient has completed adjuvant and radiotherapy, including trastuzumab, and is asymptomatic. The authors believed this to be the first demonstration of Her-2/neu amplification in a malignant skin adnexal tumor. In analogy to breast carcinoma, these findings suggested the applicability of trastuzumab for patients with metastatic adnexal carcinomas demonstrating Her-2/neu amplification. The role of trastuzumab, if any, for the treatment of dermal adnexal carcinoma needs to be validated by well-designed studies.

Inman et al (2003) noted that currently available systemic therapies for malignant melanoma produce low response rates in patients, and more effective treatment modalities are clearly needed. Trastuzumab has had a significant impact on therapy for patients with HER2-over-expressing metastatic breast cancer. This study examined the incidences of HER2 protein over-expression and HER2 gene amplification in metastatic malignant melanoma, which
remain unclear in the literature. The study evaluated patients with stage III and stage IV malignant melanoma who were treated between 1983 and 1999. Tissue blocks were retrieved and reviewed to confirm the diagnosis. From the 101 cases identified, 49 (31 stage III and 18 stage IV) had sufficient residual tumor sample to enable an assay to be performed. The blocks were tested for HER2 over-expression using the DAKO HercepTest immunohistochemical (IHC) assay. Any sample that tested 1+ or greater for HER2 expression on IHC and a randomly selected subset of HER2-negative samples were tested for the presence of HER2 gene amplification using the Vysis PathVysion fluorescence in situ hybridization (FISH) assay. The median age of the 49 selected patients was 52.2 years, and the male-to-female ratio was 1.23:1 (27 men to 22 women). All of the 49 cases of malignant melanoma were negative for HER2 over-expression by IHC. However, 2 samples (3 %) were found to have a weak level of HER2 expression (1+ level of staining). Subsequent FISH results on the samples that were 1+ on IHC were negative for HER2 gene amplification. FISH results on 21 other randomly selected IHC-negative samples were also negative for HER2 amplification. Flow cytometry failed to show HER2 over-expression in 2 melanoma cell lines, and treatment of these cells with trastuzumab did not affect their proliferation rate. These researchers found a low incidence of HER2 expression and no evidence of HER2 protein over-expression or HER2 gene amplification in metastatic malignant melanoma tissues. Therefore, routine testing for HER2 over-expression or HER2 amplification would not be of benefit in this patient population. These results also imply that anti-HER2 therapy with trastuzumab is highly unlikely to provide benefit for patients with metastatic melanoma.

Kluger et al (2004) noted that melanoma is among the most chemotherapy-resistant malignancies. Numerous new agents have been developed that target specific molecules on cancer cells, including the monoclonal antibody trastuzumab, which targets Her2/neu and has been very beneficial in the treatment of breast cancer. There are conflicting reports in the literature about Her2/neu expression in melanoma specimens, but all of the cohorts studied have been small. These researchers therefore examined Her2/neu expression in a very large cohort of melanoma specimens in order to determine the value of exploring trastuzumab therapy for melanoma patients. Immunohistochemical staining was performed on 2 tissue microarrays, together containing 600 intact specimens. Expression was evaluated semi-quantitatively and correlated with tumor stage and other clinicopathological data. Of the 600 specimens in the cohort, 31 patients (5.2 %) had positive Her2/neu expression. Among the primary cutaneous specimens (n = 269), 7 % had positive Her2/neu staining, while 3.6 % of the recurrent or metastatic specimens (n = 331) had positive Her2/neu staining (p = 0.06). Among the primary lesions there was no significant correlation between Her2/neu expression, Clark level and ulceration; however, Her2/neu expression was associated with lesions with a Breslow depth of less than 2 mm (p = 0.05). Using this very large cohort of melanoma specimens, these researchers found only a few cases with aberrant Her2/neu expression, many of them being primary cutaneous lesions rather than recurrent or metastatic lesions. The authors concluded that these findings suggested that drugs that specifically target Her2/neu are not likely to be useful for the treatment of metastatic melanoma or as adjuvant therapy for melanoma patients at high risk for recurrence.

In a phase II clinical trial, Ebb and colleagues (2012) examined the safety and feasibility of delivering biologically targeted therapy by combining trastuzumab with standard chemotherapy in patients with metastatic osteosarcoma and HER2 over-expression. Among 96 evaluable patients with newly diagnosed metastatic osteosarcoma, 41 had tumors that were HER2-positive by immunohistochemistry. All patients received chemotherapy with cisplatin, doxorubicin, methotrexate, ifosfamide, and etoposide. Dexrazoxane was administered with doxorubicin to minimize the risk of cardiotoxicity from treatment with trastuzumab and anthracycline. Only patients with HER2 over-expression received concurrent therapy with trastuzumab given for 34 consecutive weeks. The 30-month event-free and OS rates for patients with HER2 over-expression treated with chemotherapy and
trastuzumab were 32% and 59%, respectively. For patients without HER2 over-expression, treated with chemotherapy alone, the 30-month event-free and OS rates were 32% and 50%, respectively. There was no clinically significant short-term cardiotoxicity in patients treated with trastuzumab and doxorubicin. The authors concluded that despite intensive chemotherapy plus trastuzumab for patients with HER2-positive disease, the outcome for all patients was poor, with no significant difference between the HER2-positive and HER2-negative groups. The authors concluded that although these findings suggested that trastuzumab can be safely delivered in combination with anthracycline-based chemotherapy and dexrazoxane, its therapeutic benefit remains uncertain. They stated that definitive assessment of trastuzumab's potential role in treating osteosarcoma would require a randomized study of patients with HER2-positive disease.

Larsen et al (2013) noted that patients with HER2-positive breast cancer are living still longer and increasingly experiencing brain metastases. Current HER2-targeted therapies have limited potential to cross the blood-brain-barrier. These researchers performed a systematic review to investigate data on HER2-targeting therapies in the treatment of brain metastases in breast cancer. They searched PUBMED for all human studies published 1998 to 2012 using the following search terms: breast neoplasm/cancer, human epidermal growth factor receptor 2/HER2, ErbB2, trastuzumab, lapatinib, brain/cerebral neoplasm/metastases and blood-brain barrier. They identified few and mostly small clinical studies. Study designs were very heterogeneous making comparisons on end-points difficult. Overall survival for patients treated with trastuzumab varied from 8 to 25 months and 5.5 to 11 months for patients receiving lapatinib. The majority of studies were retrospective, thus possibly biasing data. Only 3 studies were identified comparing trastuzumab to lapatinib. The authors concluded that no solid data exist on how to treat patients with HER2-positive disease and brain metastases. Although continuous HER2-blockade is recommended by international consensus guidelines, it is still not evident which HER2-targeting agent should be preferred when brain metastases occur. The choice of chemotherapy to accompany the blockade is not obvious and these investigators do not know if dual is better than single blockade. They stated that further clinical trials are urgently needed.

Zagouri et al (2013) stated that leptomeningeal carcinomatosis (MC) represents an uncommon, but devastating manifestation of metastatic breast cancer. This was the first systematic review/pooled analysis to synthesize all available data evaluating the safety and effectiveness of intra-thecal (IT) administration of trastuzumab for the treatment of MC in HER2-positive breast cancer patients. This study was performed in accordance with the PRISMA guidelines. A total of 13 articles (17 patients) were eligible. The mean age of patients at IT trastuzumab administration was 48.2 years (SD 8.4, range of 38 to 66). The mean total dose was 399.8 mg (SD 325.4, range of 35 to 1,110 mg). Intra-thecal trastuzumab alone or as part of combination therapies seemed to be safe; no serious adverse events were reported in 88.2% of cases. In 68.8% of cases, a significant clinical improvement was observed, while stabilization or progression of the disease was noticed in 31.2% of cases. Cerebrospinal fluid (CSF) response was noted in 66.7% of cases. The median OS was 13.5 months, whereas the median central nervous system-progression-free survival (CNS-PFS) was 7.5 months. In 23.5% of cases, IT trastuzumab was administered beyond CNS progression with a response noticed in 75% of cases and a CNS-PFS of 9.4 months. The cumulative dose of IT trastuzumab given was 1,040 mg (SD 697.9, median of 1,215, range of 55 to 1,675). The protective effect of prior radiosurgery or neurosurgery upon CNS-PFS was sizeable but did not reach formal statistical significance (HR 0.28, 95% CI: 0.06 to 1.37). Clinical improvement (HR 0.14, 95% CI: 0.02 to 0.91) and CSF response (HR 0.09, 95% CI: 0.01 to 0.89) were associated with longer CNS-PFS. The authors concluded that IT administration seems to represent a safe and in some cases effective option for the treatment of HER2-positive breast cancer patients with leptomeningeal involvement. Moreover, they stated that clinical trials are urgently needed to establish the definite role of IT trastuzumab in HER2-positive metastatic breast cancer patients with MC.
Furthermore, the NCCN’s clinical practice guideline on “Central nervous system cancers” (Version 2.2013) does not mention the use of trastuzumab or trastuzumab as a therapeutic option.

Goldhirsch and colleagues (2013) stated that trastuzumab has established effectiveness against breast cancer with over-expression or amplification of the HER2 oncogene. The standard of care is 1 year of adjuvant trastuzumab, but the optimum duration of treatment is unknown. In an open-label, RCT, these investigators compared 2 years of treatment with trastuzumab with 1 year of treatment, and updated the comparison of 1 year of trastuzumab versus observation at a median follow-up of 8 years, for patients enrolled in the HERceptin Adjuvant (HERA) trial. The HERA trial was an international, multi-center, randomized, open-label, phase III clinical trial comparing treatment with trastuzumab for 1 and 2 years with observation after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both in 5,102 patients with HER2-positive early breast cancer. The primary end-point was DFS. The comparison of 2 years versus 1 year of trastuzumab treatment involved a landmark analysis of 3,105 patients who were disease-free 12 months after randomization to one of the trastuzumab groups, and was planned after observing at least 725 DFS events. The updated intention-to-treat comparison of 1 year trastuzumab treatment versus observation alone in 3,399 patients at a median follow-up of 8 years (range of 0 to 10) was also reported. These researchers recorded 367 events of DFS in 1,552 patients in the 1 year group and 367 events in 1,553 patients in the 2 year group (HR 0.99, 95 % CI: 0.85 to 1.14, p = 0.86).

Grade 3 to 4 adverse events and decreases in left ventricular ejection fraction (LVEF) during treatment were reported more frequently in the 2 year treatment group than in the 1 year group (342 [20.4 %] versus 275 [16.3 %] grade 3 to 4 adverse events, and 120 [7.2 %] versus 69 [4.1 %] decreases in LVEF, respectively). Hazard ratios for a comparison of 1 year of trastuzumab treatment versus observation were 0.76 (95 % CI: 0.67 to 0.86, p < 0.0001) for DFS and 0.76 (0.65 to 0.88, p = 0.0005) for OS, despite cross-over of 884 (52 %) patients from the observation group to trastuzumab therapy. The authors concluded that 2 years of adjuvant trastuzumab is not more effective than is 1 year of treatment for patients with HER2-positive early breast cancer. Moreover, 1 year of treatment provided a significant DFS and OS benefit compared with observation and remains the standard of care.

Pivot and associates (2013) noted that since 2005, 12 months of adjuvant trastuzumab has been the standard treatment for patients with HER2-positive early-stage breast cancer. However, the optimum duration of treatment has been debated. These investigators performed a non-inferiority trial of a shorter exposure of 6 months versus the standard 12 months of trastuzumab for patients with early breast cancer. They did an open-label, randomized, phase III clinical trial in 156 centers in France. Patients with HER2-positive early breast cancer who had received at least 4 cycles of chemotherapy, had breast-axillary surgery, and had received up to 6 months of trastuzumab (administered by intravenous infusions over 30 to 90 mins every 3 weeks; initial loading dose 8 mg/kg; 6 mg/kg thereafter) before randomization were eligible. Patients were randomly assigned via central randomization procedure with web-based software to continue trastuzumab for another 6 months (12 months total duration; control group) or to discontinue trastuzumab at 6 months (6 months total duration; experimental group). Randomization was stratified by concomitant or sequential administration of trastuzumab with chemotherapy, estrogen-receptor status, and center using a minimization algorithm. The primary end-point was DFS, with a pre-specified non-inferiority margin of 1.15. Analyses were carried out in the intention-to-treat population. A total of 1,691 patients were randomly assigned to receive 12 months of trastuzumab and 1,693 to receive 6 months of trastuzumab; 1,690 patients in each group were included in the intention-to-treat analyses. After a median follow-up of 42.5 months (IQR 30.1 to 51.6), 175 DFS events were noted in the 12-month group and 219 in the 6-month group; 2-year DFS was 93.8 % (95 % CI: 92.6 to 94.9) in the 12-month group and 91.1 % (89.7 to 92.4) in the 6-month group (HR 1.28, 95 % CI: 1.05 to 1.56; p = 0.29). 119 (93 %)
of the 128 cardiac events (clinical or based on assessment of LVEF) occurred while patients were receiving trastuzumab. Significantly more patients in the 12-month group experienced a cardiac event than did those in the 6-month group (96 [5.7 %] of 1690 patients versus 32 [1.9 %] of 1,690 patients, p < 0.0001). The authors concluded that after 3.5 years follow-up, they failed to show that 6 months of treatment with trastuzumab was non-inferior to 12 months of trastuzumab. Moreover, they stated that despite the higher rates of cardiac events, 12 months of adjuvant trastuzumab should remain the standard of care.

Sorscher (2013) stated that trastuzumab is a monoclonal antibody targeting HER-2; and HER -2 over-expression has been described in gallbladder cancer and in cholangiocarcinoma. The author described the first case of a patient with HER-2 over-expressing metastatic gallbladder adenocarcinoma and responding radiographically and biochemically to trastuzumab alone. The finding of this case study needs to be validated by well-designed studies. Moreover, the NCCN's clinical practice guideline on “Hepatobiliary cancers” (Version 1.2014) does not mention the use of trastuzumab, pertuzumab, or ado-trastuzumab emtansine as a therapeutic option.

Although cervical neuroendocrine tumors are rare, they are addressed in the NCCN guidelines on “Neuroendocrine tumors” (Version 1.2015), which state that the classic small cell neuroendocrine tumor is poorly differentiated and occurs in the lung. They note that, although rare, extra-pulmonary large or small cell neuroendocrine tumors occur in a wide variety of organs. The NCCN guidelines state that the cervix is the most common extra-pulmonary location of these tumors, followed by the esophagus, larynx and pharynx, colon and rectum, and prostate. For chemotherapy of these large and small cell neuroendocrine tumors, the NCCN guidelines recommend chemotherapy with a small cell lung cancer regimen. They note that, in general, cisplatin or carboplatin and etoposide are recommended as primary treatment. The NCCN Compendium has no recommendation for use of trastuzumab (Herceptin) for small cell lung cancer or neuroendocrine tumors.

The authors of an UpToDate chapter on “Small cell neuroendocrine carcinoma of the cervix” state that they administer a similar chemotherapy regimen as the one used for small cell lung cancer such as etoposide plus cisplatin (Leitao and Zivanovic, 2015).

An UpToDate review on “Ampullary carcinoma: Treatment and prognosis” (Ryan et al, 2015) does not mention the use of trastuzumab as a therapeutic option.

Furthermore, NCCN’s Drugs & Biologic Compendium (2015) does not list ampullary adenocarcinoma and intra-hepatic bile duct cancer as recommended indications of trastuzumab.

Pertuzumab (Perjeta):

Pertuzumab is a new anti-HER2 humanized monoclonal antibody that prevents the formation of HER2 dimers. It is the first HER dimerization inhibitor that the mechanism of action is complementary to trastuzumab. Pertuzumab is administered intravenously and is believed to work by targeting a different part of the HER-protein than trastuzumab, resulting in further reduction in growth and survival of HER2-positive breast cancer cells. The safety and effectiveness of Perjeta were evaluated in a single clinical trial involving 808 patients with HER2-positive metastatic breast cancer who were tested prior to treatment to determine if the HER2 protein was increased. Patients were randomly assigned to receive Perjeta, trastuzumab and docetaxel or trastuzumab and docetaxel with a placebo. The study was designed to measure the length of time a patient lived without the cancer progressing, progression-free survival (PFS). Those treated with the combination containing Perjeta had a median PFS of 18.5 months, while those treated with the combination containing placebo had a median PFS of 12.4 months. The most common side effects observed in patients receiving Perjeta in combination with trastuzumab and docetaxel were diarrhea, fatigue, hair loss, leukopenia, nausea, rash, and peripheral sensory neuropathy.
On June 8, 2012, the FDA approved pertuzumab (Perjeta) for the treatment of patients with HER2-positive metastatic breast cancer. Pertuzumab, in combination with trastuzumab and docetaxel, is indicated for patients who have not received prior treatment for metastatic breast cancer with an anti-HER2 therapy or chemotherapy.

The NCCN's Drugs & Biologics Compendium (2012) recommends pertuzumab for recurrent or metastatic HER2-positive disease that is either hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory or with symptomatic visceral disease as preferred 1st-line therapy in combination with trastuzumab with docetaxel or paclitaxel. According to NCCN, pertuzumab may be considered in combination with trastuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy beyond 1st-line therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab.

Pertuzumab has also been studied for the treatment of other types of solid tumors (e.g., colon, gastric, lung, ovarian, prostate, rectal, and uterine cancers); however, its effectiveness for these types of cancer has not been established.

Pohl et al (2009) examined the anti-tumor activity of pertuzumab as a single agent or in combination with erlotinib or irinotecan in human colon cancer cells in-vitro and in-vivo. Colon cancer cell lines were tested for HER1/HER2 expression by western blot analysis. The effect of pertuzumab on cell cycle distribution was analyzed by FACS. Nude mice bearing xenograft tumors were treated with pertuzumab alone, or in combination either with irinotecan or with erlotinib. Tumor volume was measured repeatedly. Tumor histology was analyzed for necrosis. Six of nine cell lines showed high expression of HER1/HER2. Pertuzumab inhibited cell cycle progression in various cell lines. Pertuzumab showed minor anti-tumor activity in xenograft tumors, but significantly inhibited tumor growth when combined with erlotinib (p < 0.001). Combination of pertuzumab with irinotecan had no additional effect on growth of additional tumors. Pertuzumab treated DLD-1 xenograft tumors did not show enhanced necrosis, which, however, was found in HCT116 derived xenografts. The authors concluded that pertuzumab has some anti-tumor activity on human colon cancer cells in-vitro and in-vivo, in particular when combined with erlotinib. In-vivo, pertuzumab combination treatment was not superior to irinotecan monotherapy. These data warrant further investigation of simultaneous HER1/EGFR TKI inhibition and HER1/HER2 dimerization inhibition for colorectal cancer therapy.

El-Sahwi et al (2010) evaluated pertuzumab activity separately or in combination with trastuzumab against primary uterine serous papillary adenocarcinoma (USPC) cell lines expressing different levels of HER2/neu. Six USPC cell lines were assessed by immunohistochemistry (IHC), flow cytometry, and real-time polymerase chain reaction for HER2/neu expression. c-erbB2 gene amplification was evaluated using fluorescent in-situ hybridization (FISH). Sensitivity to pertuzumab and trastuzumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) was evaluated in 5 h chromium release assays. Pertuzumab cytostatic activity was evaluated using proliferation-based assays. Three USPC cell lines stained heavily for HER2/neu by IHC and showed amplification of the c-erbB2 gene by FISH. The remaining FISH-negative USPCs expressed HER2/neu at 0/1+ levels. In cytotoxicity experiments against USPC with a high HER2/neu expression, pertuzumab and trastuzumab were similarly effective in inducing strong ADCC. The addition of complement-containing plasma and interleukin-2 increased the cytotoxic effect induced by both mAbs. In low HER2/neu USPC expressors, trastuzumab was more potent than pertuzumab in inducing ADCC. Importantly, in this setting, the combination of pertuzumab with trastuzumab significantly increased the ADCC effect induced by trastuzumab alone (p = 0.02). Finally, pertuzumab induced a significant inhibition in the proliferation of all USPC cell lines tested, regardless of their HER-2/neu expression. The authors concluded that pertuzumab and trastuzumab induce equally
strong ADCC and CDC in FISH-positive USPC cell lines. Pertuzumab significantly increases trastuzumab-induced ADCC against USPC with a low HER2/neu expression and may represent a new therapeutic agent in patients harboring advanced/recurrent and/or refractory USPC.

In a Cochrane review, Haldar et al (2011) compared the effectiveness and toxicities of epidermal growth factor receptor (EGFR) inhibitors alone or in combination with standard chemotherapy in the treatment of ovarian cancer. These investigators searched the Cochrane Gynaecological Cancer Group Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 4, 2010, MEDLINE and EMBASE up to October 2010. They also searched registers of clinical trials, abstracts of scientific meetings, and reference lists of included studies, and contacted experts in the field. Randomized controlled trials (RCTs) comparing anti-EGFR agents with or without conventional chemotherapy versus conventional chemotherapy alone or no treatment in women with histologically proven ovarian cancer. Two review authors independently abstracted data and assessed risk of bias. They reported adjusted HRs for OS and PFS and risk ratios (RRs) comparing adverse events in women who received gemcitabine plus pertuzumab and gemcitabine plus placebo. These researchers found only 1 completed and 3 ongoing RCTs that met their inclusion criteria. The completed trial randomized 131 women with relapsed ovarian cancer to receive gemcitabine and pertuzumab or placebo and gemcitabine (control). There was no statistically significant difference in OS, PFS and response between women who received gemcitabine and pertuzumab and those who received control, although PFS approached borderline significance (adjusted HR = 0.66, 95 % CI: 0.43 to 1.03; p = 0.06). The trial reported a higher rate of adverse events in the gemcitabine and pertuzumab arm for most outcomes, but most were not statistically significant (although many approached borderline significance) because the trial lacked statistical power due to its relatively small size and the low number of observed events. The trial was at moderate risk of bias. The authors concluded that EGFR inhibitors, including pertuzumab, may add activity to conventional chemotherapy for treatment of platinum-resistant ovarian cancer. Certain subsets of women with particularly aggressive tumors resistant to conventional chemotherapy may benefit from EGFR inhibitor treatment. They stated that further RCTs are needed before EGFR inhibitors are introduced as first- or second-line treatment of ovarian cancer.

In a phase II clinical trial, Kaye et al (2013) evaluated the safety and effectiveness of pertuzumab in combination with carboplatin-based chemotherapy in patients with platinum-sensitive, recurrent advanced ovarian cancer. Patients were randomized to receive 6 cycles of chemotherapy (carboplatin and either paclitaxel (Taxol) or gemcitabine) with or without pertuzumab. The primary end point was PFS as determined by Response Evaluation Criteria in Solid Tumors and/or by CA 125 measurements. Secondary end points evaluated the response rate, safety profile, duration of response, time to PFS and OS for both treatment arms. A total of 149 patients received either chemotherapy with pertuzumab (arm A, n = 74) or chemotherapy alone (arm B, n = 75). There was no significant difference either in median PFS or in the secondary end points between the 2 arms. No differences were seen in an exploratory biomarker analysis of HER3 mRNA expression between the 2 arms. Pertuzumab was well-tolerated, with no increase in cardiac adverse events compared with chemotherapy alone. The authors concluded that addition of pertuzumab to carboplatin-based chemotherapy did not substantially prolong PFS in unselected patients with platinum-sensitive ovarian cancer.

Malara et al (2012) noted that prostate cancer is the most commonly diagnosed malignancy in men in developed countries. ErbB2, a tyrosine kinase receptor over-expressed in many human cancer types, contributes to prostate cancer progression by activating the androgen receptor in a steroid poor environment, thus promoting androgen-independent cell growth. The consequent development of hormone refractory tumors is a major obstacle in prostate cancer therapy. The inhibition of ErbB2 signal transduction pathways by the use of human
antibodies could be a valuable alternative strategy for cancer therapy. These investigators performed a comparative analysis in-vitro and in-vivo of the anti-tumor effects of 3 different antibodies targeting different epitopes of ErbB2: Herceptin (trastuzumab), 2C4 (pertuzumab) and Erb-hcAb (human anti-ErbB2-compact antibody), a novel fully human compact antibody. These researchers demonstrated that the growth of both androgen-dependent and independent prostate cancer cells was efficiently inhibited by Erb-hcAb. The anti-tumor effects induced by Erb-hcAb on some cell lines were more potent than those observed for either Herceptin or 2C4. Thus, Erb-hcAb could be a promising candidate in the immunotherapy of prostate cancer for which no obvious treatment has been reported so far.

Felip et al (2012) stated that pertuzumab has demonstrated pharmacodynamics activity with stable disease in non-small-cell lung cancer (NSCLC). Combining erlotinib and pertuzumab may enhance antitumor activity. These researchers aimed to establish the recommended dosing of the erlotinib and pertuzumab combination; assessed safety, preliminary efficacy, and pharmacokinetics; and analyzed biomarkers. A total of 15 patients with stage IIIb/IV NSCLC who failed chemotherapy were recruited. The patients received erlotinib (days -8 to -1), then combination therapy (21-day cycles for 6 cycles). Pertuzumab was given intravenously at 840 mg, then 420 mg once every 3 weeks, with erlotinib given daily (100 or 150 mg). No dose-limiting toxicities were observed. Adverse events were generally grade 1/2 and manageable. The objective response rate was 20 % (3/15 patients; 2 responders had mutant HER1, 1 responder had wild-type HER1), median overall PFS was 9.3 weeks. High HER1, HER2, and HER3 messenger RNA expression correlated with increased PFS. Combination therapy did not affect erlotinib’s pharmacokinetics; however, pertuzumab mean exposures (maximum concentration, 231 mg/L; area under the concentration-time curve from 0 to 21 days, 1,780 mg d/L) were slightly higher than in previous studies. The authors concluded that combination therapy was well-tolerated in patients with good performance status, with encouraging efficacy.

Pazo Cid and Anton (2013) stated that the prognostic value of HER2 in gastric cancer is controversial. Consensus guidelines have standardized the testing of HER2 status in gastric cancer. Over-expression of this receptor occurs in approximately 20 % of gastric and gastro-esophageal junction adenocarcinomas, predominantly those of the intestinal type. Recently, trastuzumab has emerged as the first targeted drug to improve OS when combined with chemotherapy in advanced HER2-positive gastric cancer. Primary and secondary resistance to trastuzumab has become a major problem and new strategies to overcome this resistance are needed. A high percentage of advanced HER2-positive gastric cancer patients who progress on trastuzumab therapy are candidates for second-line therapy. New families of targeted drugs, including tyrosine kinase inhibitors (TKIs) such as lapatinib and PF-00299804, mammalian target of rapamycin (mTOR) pathway inhibitors such as everolimus, heat-shock protein 90 (HSP90) inhibitors such as AUY922, HER dimerization inhibitors such as pertuzumab, and antibody-chemotherapy conjugates such as trastuzumab-emtansine (T-DM1), could offer alternative second-line treatments when trastuzumab-based first-line therapy fails.

Neoadjuvant systemic therapy is frequently used option for the systemic treatment for breast cancer. Inclusion in the regimen of targeted drugs (e.g., trastuzumab and pertuzumab) significantly improves outcomes in HER2-positive breast cancer patients (Semiglazov et al, 2013). O’Sullivan and Swain (2013) noted that HER2 over-expression or amplification is present in approximately 1/5 of breast cancers and historically was associated with aggressive disease and poorer prognosis. The introduction of the humanized monoclonal antibody trastuzumab dramatically improved DFS and OS in this subgroup. As the majority of patients with metastatic disease ultimately develop resistance to trastuzumab, a need exists for more effective targeted therapies. Pertuzumab is an anti-HER2/neu-targeted therapy in the late stages of clinical development. The combination of pertuzumab, trastuzumab and docetaxel has been found to have an OS benefit in patients with HER2
positive MBC when used in the first-line setting. This reflects a new standard of care, and pertuzumab was recently approved for this indication by the FDA. The effectiveness of pertuzumab and trastuzumab in conjunction with chemotherapy is currently being evaluated in the adjuvant setting.

Zagouri et al (2013) carried out the first systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to synthesize all available data of pertuzumab in breast cancer. The search strategy retrieved 11 studies that evaluated pertuzumab. One study was conducted in the neoadjuvant setting (417 patients), whereas all the others dealt with patients with recurrent, metastatic, or refractory disease (1,023 patients). Six studies were conducted in HER2(+) breast cancer population (1,354 patients), whereas 5 studies (86 patients) were conducted in HER2(-) (or unknown HER2 status) disease.

Pertuzumab is the most recent agent approved by the FDA in combination with trastuzumab and docetaxel for the treatment of patients with HER2(+) metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. This approval has been based on data from a phase III Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study. The anti-tumor activity with the significant reduction in the risk of progression or death, as reflected upon the increase of 6.1 months in median PFS, indicates that pertuzumab may provide an avenue for achieving additional benefit for patients with HER2(+). Moreover, pertuzumab seems to have a putative role in the management of patients with HER2 who are resistant to trastuzumab. The promising role of pertuzumab in the neoadjuvant and adjuvant settings remains to be further investigated and established in the future.

In a randomized, multi-center, open-label, phase II study, Gianni et al (2012) examined the combination of pertuzumab or trastuzumab, or both, with docetaxel and the combination of pertuzumab and trastuzumab without chemotherapy in the neoadjuvant setting. Treatment-naive women with HER2-positive breast cancer were randomly assigned (1:1:1:1) centrally and stratified by operable, locally advanced, and inflammatory breast cancer, and by hormone receptor expression to receive 4 neoadjuvant cycles of: trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus docetaxel (75 mg/m(2), escalating, if tolerated, to 100 mg/m(2) every 3 weeks; group A) or pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel (group B) or pertuzumab and trastuzumab (group C) or pertuzumab plus docetaxel (group D). The primary end-point, examined in the intention-to-treat population, was pathological complete response (pCR) in the breast. Neither patients nor investigators were masked to treatment. Of 417 eligible patients, 107 were randomly assigned to group A, 107 to group B, 107 to group C, and 96 to group D. Patients given pertuzumab and trastuzumab plus docetaxel (group B) had a significantly improved pCR rate (49 of 107 patients; 45.8 % [95 % CI: 36.1 to 55.7]) compared with those given trastuzumab plus docetaxel (group A; 31 of 107; 29.0 % [20.6 to 38.5]; p = 0.0141); 23 of 96 (24.0 % [15.8 to 33.7]) women given pertuzumab plus docetaxel (group D) had a pCR, as did 18 of 107 (16.8 % [10.3 to 25.3]) given pertuzumab and trastuzumab (group C). The most common adverse events of grade 3 or higher were neutropenia (61 of 107 women in group A, 48 of 107 in group B, 1 of 108 in group C, and 52 of 94 in group D), febrile neutropenia (8, 9, 0, and 7, respectively), and leucopenia (13, 5, 0, and 7, respectively). The number of serious adverse events was similar in groups A, B, and D (15 to 20 serious adverse events per group in 10 to 17 % of patients) but lower in group C (4 serious adverse events in 4 % of patients). The authors concluded that patients given pertuzumab and trastuzumab plus docetaxel (group B) had a significantly improved pCR rate compared with those given trastuzumab plus docetaxel, without substantial differences in tolerability. Pertuzumab and trastuzumab without chemotherapy eradicated tumors in a proportion of women and showed a favorable safety profile. The authors stated that these findings justified further exploration in adjuvant trials and support the neoadjuvant approach for accelerating drug assessment in early breast cancer.
In a randomized phase II clinical trial, Schneeweiss et al (2013) evaluated the tolerability, with particular focus on cardiac safety, of trastuzumab and pertuzumab (P) with chemotherapy in the neoadjuvant treatment of HER2-positive early breast cancer. In this multi-center, open-label phase II study, patients with operable, locally advanced, or inflammatory breast cancer were randomized 1 : 1 to receive 6 neoadjuvant cycles q3w (Arm A: 5-fluorouracil, epirubicin, cyclophosphamide [FEC] + H + P ×3 → docetaxel [T] + H + P ×3; Arm B: FEC ×3 → T + H + P ×3; Arm C: T + carboplatin + H [TCH]+P ×6). Pathologic complete response was assessed at surgery and adjuvant therapy given to complete 1 year of H. A total of 225 patients were randomized. During neoadjuvant treatment, 2 patients (2.7 %; Arm B) experienced symptomatic left ventricular systolic dysfunction (LVSD) and 11 patients (Arm A: 4 [5.6 %]; Arm B: 4 [5.3 %]; Arm C: 3 [3.9 %]) had declines in left ventricular ejection fraction of greater than or equal to 10 % points from baseline to less than 50 %. Diarrhea was the most common adverse event. Pathologic complete response (ypT0/is) was reported for 61.6 % (Arm A), 57.3 % (Arm B), and 66.2 % (Arm C) of patients. The authors concluded that the combination of P with H and standard chemotherapy resulted in low rates of symptomatic LVSD.

On September 30, 2013, the FDA granted accelerated approval to Perjeta (pertuzumab) as part of a complete treatment regimen for patients with early stage breast cancer before surgery (neoadjuvant setting). Perjeta is the 1st FDA-approved drug for the neoadjuvant treatment of breast cancer. Perjeta's new indication is intended for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer (tumor greater than 2 cm in diameter or with positive lymph nodes) who are at high risk of having their cancer return or metastasize or of dying from the disease. It is to be used in combination with trastuzumab and other chemotherapy prior to surgery and, depending upon the treatment regimen used, may be followed by chemotherapy after surgery. Following surgery, patients should continue to receive trastuzumab to complete 1 year of treatment. Perjeta’s accelerated approval for neoadjuvant treatment is based on a study designed to measure pCR. In the study, 417 subjects were randomly assigned to receive 1 of 4 neoadjuvant treatment regimens: (i) trastuzumab plus docetaxel, (ii) Perjeta plus trastuzumab and docetaxel, (iii) Perjeta plus trastuzumab, or (iv) Perjeta plus docetaxel. About 39 % of subjects who received Perjeta plus trastuzumab and docetaxel achieved pCR, compared to about 21 % who received trastuzumab plus docetaxel. The confirmatory trial for this accelerated approval is being conducted in patients with HER2-positive breast cancer who had prior breast cancer surgery and are at high risk of having their cancer return. More than 4,800 participants are enrolled in this trial, which will provide further data on safety, effectiveness, and long-term outcomes. Results are expected in 2016.

Swain et al (2013) noted that CLEOPATRA is a phase III study to compare the safety and effectiveness of pertuzumab, trastuzumab, and docetaxel with placebo, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer. The results of the primary analysis showed significantly longer median PFS in the pertuzumab group than in the placebo group. Interim analysis of OS favored the pertuzumab group but was not significant. These researchers reported results for OS after an additional year of follow-up. The study was a double-blind randomized trial undertaken at 204 centers in 25 countries. Patients with HER2-positive metastatic breast cancer who had not received previous chemotherapy or biological treatment for their metastatic disease were randomly assigned to receive either (i) pertuzumab, trastuzumab plus docetaxel (n = 402); or (ii) the same regimen with a matching placebo replacing pertuzumab (n = 406). Randomization was in a 1:1 ratio, stratified by geographical region and previous treatment status. The primary end-point was PFS (assessed independently), which has been reported previously; no follow-up data were gathered for the primary end-point. Secondary end-points included OS, PFS (assessed by investigator), objective response rate, and safety. Median follow-up was 30 months in both groups. Effectiveness end-points were analyzed in the intention-to-treat population and
safety was analyzed by treatment received. The study was completed but safety and survival data continue to be followed-up. In the intention-to-treat population, 267 patients died by data cut-off (May 14, 2012), 154 (38 %) of 406 in the placebo group and 113 (28 %) of 402 in the pertuzumab group. Median OS was 37.6 months (95 % CI: 34. To -NE [not estimable]) in the placebo group but had not been reached (95 % CI: 42.4 to NE) in the pertuzumab group (HR 0.66, 95 % CI: 0.52 to 0.84; p = 0.0008). Investigator-assessed median PFS was 12.4 months (95 % CI: 10.4 to 13.5) in the placebo group and 18.7 months (16.6 to 21.6) in the pertuzumab group (HR 0.69, 95 % CI: 0.58 to 0.81). Serious adverse events were reported in 115 (29 %) of 396 patients who received placebo, trastuzumab, and docetaxel and 148 (36 %) of 408 who received pertuzumab, trastuzumab, and docetaxel, and included febrile neutropenia, neutropenia, diarrhea, pneumonia, and cellulitis. Overall, adverse events were similar to those reported at the primary analysis with respect to frequency, severity, and specificity. The authors concluded that their analysis showed a significant improvement in OS with pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive metastatic breast cancer, compared with placebo, trastuzumab, and docetaxel. Moreover, they stated that since this effect was not achieved at the expense of adverse events, this regimen represents a substantial improvement on the standard of care for this population of patients.

Kumler et al (2014) stated that HER2 is over-expressed in 15 to 20 % of all breast cancers. Treatment with trastuzumab has led to an improved outcome and prolonged survival of HER2 -positive breast cancer patients and today the drug is established as standard of care in both the adjuvant and metastatic settings. However, trastuzumab resistance is common and a major focus in the treatment of HER2-positive breast cancer has been developing therapeutic agents to either potentiate the effect of trastuzumab or to target cells which have become resistant to trastuzumab. These investigators examined the effectiveness and toxicity of dual targeting in HER2-positive breast cancer. A computer-based literature search was carried out using PubMed; data reported at international meetings and clinicaltrials.gov was included. This paper described safety and effectiveness of lapatinib, pertuzumab or trastuzumab-DM1 in combination with trastuzumab in the (neo)adjuvant and metastatic settings. Furthermore, combinations of trastuzumab and drugs targeting the downstream pathway were described. The authors concluded that dual blockade is likely to represent a substantial advance for patients with HER2-positive breast cancer. However, the relevant subpopulation remains to be defined and side effects including cardiotoxicity might be a limiting factor to the use. They stated that there is an urgent need for prospective biomarker- driven trials to identify patients for whom dual targeting is cost-effective.

Thomas et al (2014) noted that the anti-HER2 antibody pertuzumab inhibits HER2 dimerization and affects HER2/HER3 dimer formation and signaling. As HER3 and its ligand neuregulin are implicated in pancreatic tumorigenesis, these researchers investigated whether HER3 expression could be a predictive biomarker of pertuzumab efficacy in HER2low-expressing pancreatic cancer. They correlated in-vitro and in-vivo HER3 expression and neuregulin dependency with the inhibitory effect of pertuzumab on cell viability and tumor progression. HER3 knockdown in BxPC-3 cells led to resistance to pertuzumab therapy. Pertuzumab treatment of HER3-expressing pancreatic cancer cells increased HER3 at the cell membrane, whereas the anti-HER3 monoclonal antibody 9F7-F11 down-regulated it. Both antibodies blocked HER3 and AKT phosphorylation and inhibited HER2/HER3 hetero-dimerization but affected differently HER2 and HER3 homo-dimers. The pertuzumab/9F7-F11 combination enhanced tumor inhibition and the median survival time in mice xenografted with HER3-expressing pancreatic cancer cells. Furthermore, HER2 and HER3 were co-expressed in 11 % and HER3 alone in 27 % of the 45 pancreatic ductal adenocarcinomas analyzed by immunohistochemistry. HER3 is essential for pertuzumab efficacy in HER2 low-expressing pancreatic cancer and HER3 expression might be a predictive biomarker of pertuzumab efficacy in such cancers. The authors concluded that further studies in clinical samples are needed to confirm these findings and the interest of combining anti-HER2 and anti-HER3 therapeutic antibodies.
Ado-Trastuzumab Emtansine (Kadcyla):

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate incorporating the HER2-targeted anti-tumor properties of trastuzumab with the targeted delivery to HER2 overexpressing cancer cells of a highly potent anti-microtubule agent, DM1 (N-methyl-N-[3-mercapto-1-oxopropyl]-l-alanine ester of maytansinol), a maytansine derivative. The antibody and the cytotoxic agent are conjugated by means of a stable linker (non-reducible thioether linker). As a conjugate, T-DM1's systemic adverse events (AEs) are significantly minimized due to its targeted delivery by trastuzumab to HER2-positive cells. Phase I and II clinical trials of T-DM1 as a single agent and in combination with paclitaxel, docetaxel and pertuzumab have shown clinical activity and a favorable safety profile in patients with HER2-positive metastatic breast cancer (MBC). Two randomized phase III trials of T-DM1 are awaiting final results; the EMILIA trial is evaluating T-DM1 compared with lapatinib plus capecitabine. The MARIANNE trial is evaluating T-DM1 plus placebo versus T-DM1 plus pertuzumab versus trastuzumab plus a taxane (Barginear et al, 2013).

Mathew and Perez (2011) reviewed the clinical data of T-DM1 in terms of safety and effectiveness, and described ongoing and future trials evaluating its potential role in the management of patients with HER2-positive MBC. Phase I and II studies showed that the maximum tolerated dose, and thus the recommended dose for T-DM1, is 3.6 mg/kg body weight given intravenously every 3 weeks. Single-arm phase Ib/II, II and a randomized phase II first-line study of T-DM1 versus the combination of trastuzumab/docetaxel all showed improved tolerability, and at least equivalent efficacy, compared with the current standard of care. Two randomized phase III registration studies are now active, evaluating this agent in the refractory and first-line HER2-positive settings. The authors concluded that T-DM1 has been shown to be a very promising agent for the targeted delivery of chemotherapy and anti-HER2 monoclonal antibody therapy for patients with HER2-positive MBC.

Burris and colleagues (2011) reported the findings of a single-arm phase II study that assessed safety and effectiveness of intravenous T-DM1 (3.6 mg/kg every 3 weeks) in patients with HER2-positive MBC who had tumor progression after prior treatment with HER2-directed therapy and who had received prior chemotherapy. With a follow-up of greater than or equal to 12 months among 112 treated patients, the ORR by independent assessment was 25.9 % (95 % CI: 18.4 % to 34.4 %). Median duration of response was not reached as a result of insufficient events (lower limit of 95 % CI: 6.2 months), and median PFS time was 4.6 months (95 % CI: 3.9 to 8.6 months). The response rates were higher among patients with confirmed HER2-positive tumors (immunohistochemistry 3+ or FISH-positive) by retrospective central testing (n = 74). Higher response rates were also observed in patients whose tumors expressed greater than or equal to median HER2 levels by quantitative reverse transcriptase PCR for HER2 expression, compared with patients who had less than median HER2 levels. T-DM1 was well-tolerated with no dose-limiting cardiotoxicity. Most adverse events (AEs) were grade 1 or 2; the most frequent grade greater than or equal to 3 AEs were hypokalemia (8.9 %), thrombocytopenia (8.0 %), and fatigue (4.5 %). The authors concluded that T-DM1 has robust single-agent activity in patients with heavily pre-treated, HER2-positive MBC and is well-tolerated at the recommended phase II dose.

In a single-arm phase II study, Krop et al (2012) examined if T-DM1 is effective in patients with HER2-positive MBC who have previously received all standard HER2-directed therapies. T-DM1 3.6 mg/kg was administered intravenously every 3 weeks to patients with HER2-positive MBC who had prior treatment with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. The primary objectives were ORR by independent review and safety. Among 110 pre-treated patients (median, 7 prior agents for MBC; median follow-up, 17.4 months), the ORR was 34.5 % (95 % CI: 26.1 % to 43.9 %), clinical benefit rate was 48.2 % (95 % CI: 38.8 % to 57.9 %), median PFS was 6.9 months (95 % CI: 4.2 to 8.4...
months), and median duration of response was 7.2 months (95 % CI: 4.6 months to not estimable). In patients with confirmed HER2-positive tumors (n = 80 by retrospective central testing), the response rate was 41.3 % (95 % CI: 30.4 % to 52.8 %), and median PFS was 7.3 months (95 % CI: 4.6 to 12.3 months). Most AEs were grades 1 to 2; the most frequent grade greater than or equal to 3 events were thrombocytopenia (9.1 %), fatigue (4.5 %), and cellulitis (3.6 %). The authors concluded that T-DM1 is well-tolerated and has single-agent activity in patients with HER2-positive MBC who have previously received both approved HER2-directed therapies and multiple chemotherapeutic agents.

Verma and colleagues (2012) randomly assigned patients with HER2-positive advanced breast cancer, who had previously been treated with trastuzumab and a taxane, to T-DM1 or lapatinib plus capecitabine. The primary end points were PFS (as assessed by independent review), OS, and safety. Secondary end points included PFS (investigator-assessed), the ORR, and the time to symptom progression. Two interim analyses of OS were conducted. Among 991 randomly assigned patients, median PFS as assessed by independent review was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine (hazard ratio for progression or death from any cause, 0.65; 95 % CI: 0.55 to 0.77; p < 0.001), and median OS at the second interim analysis crossed the stopping boundary for efficacy (30.9 months versus 25.1 months; hazard ratio for death from any cause, 0.68; 95 % CI: 0.55 to 0.85; p < 0.001). The ORR was higher with T-DM1 (43.6 %, versus 30.8 % with lapatinib plus capecitabine; p < 0.001); results for all additional secondary end points favored T-DM1. Rates of grade 3 or 4 AEs were higher with lapatinib plus capecitabine than with T-DM1 (57 % versus 41 %). The incidences of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1, whereas the incidences of diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus capecitabine. The authors concluded that T-DM1 significantly prolonged PFS and OS with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane.

In a phase II clinical trial, Hurvitz et al (2013) compared the effects of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with HER 2-positive MBC. Patients (n = 137) with HER2-positive MBC or recurrent locally advanced breast cancer were randomly assigned to trastuzumab plus docetaxel (HT; n = 70) or T-DM1 (n = 67) as first-line treatment until disease progression or unacceptable toxicity. Primary end points were investigator-assessed PFS and safety. Key secondary end points included OS, ORR, duration of objective response, clinical benefit rate, and quality of life. Median PFS was 9.2 months with HT and 14.2 months with T-DM1 (hazard ratio, 0.59; 95 % CI: 0.36 to 0.97); median follow-up was approximately 14 months in both arms. Objective response rate was 58.0 % (95 % CI: 45.5 % to 69.2 %) with HT and 64.2 % (95 % CI: 51.8 % to 74.8 %) with T-DM1. T-DM1 had a favorable safety profile versus HT, with fewer grade greater than or equal to 3 AEs (46.4 % versus 90.9 %), AEs leading to treatment discontinuations (7.2 % versus 40.9 %), and serious AEs (20.3 % versus 25.8 %). Preliminary OS results were similar between treatment arms; median follow-up was approximately 23 months in both arms. The authors concluded that in this randomized phase II study, first-line treatment with T-DM1 for patients with HER2-positive MBC provided a significant improvement in PFS, with a favorable safety profile, versus HT.

On February 22, 2013, the FDA approved ado-trastuzumab emtansine (Kadcyla) for the treatment of patients with HER2-positive MBC and who were previously treated with trastuzumab and taxanes. Referred to as T-DM1 during clinical research, Kadcyla was reviewed under the FDA’s priority review program, which provides for an expedited 6-month review of drugs that may provide safe and effective therapy when no satisfactory alternative therapy exists, or offer significant improvement compared to marketed products. Other FDA-approved drugs used to treat HER2-positive breast cancer include trastuzumab (1998), lapatinib (2007) and pertuzumab (2012). The safety and effectiveness of Kadcyla were
evaluated in a clinical study of 991 patients randomly assigned to receive Kadcyla or lapatinib plus capecitabine. Patients received treatment until either the cancer progressed or the AEs became intolerable. The study was designed to measure PFS and OS. Results showed that patients treated with Kadcyla had a median PFS of 9.6 months compared to 6.4 months in patients treated with lapatinib plus capecitabine. The median OS was 30.9 months in the Kadcyla group and 25.1 months in the lapatinib plus capecitabine group. The most common AEs reported in patients treated with Kadcyla were constipation, fatigue, headache, elevated levels of liver enzymes, nausea, pain in the muscles or joints, and thrombocytopenia. Kadcyla is being approved with a “Boxed Warning” alerting patients and health care professionals that the drug can cause liver toxicity, heart toxicity and death. The drug can also cause severe life-threatening birth defects, and pregnancy status should be verified prior to starting Kadcyla treatment.

Pazo Cid and Anton (2013) stated that trastuzumab has emerged as the first targeted drug to improve OS when combined with chemotherapy in advanced HER2-positive gastric cancer. Primary and secondary resistance to trastuzumab has become a major problem and new strategies to overcome this resistance are needed. A high percentage of advanced HER2-positive gastric cancer patients who progress on trastuzumab therapy are candidates for second-line therapy. New families of targeted drugs, including tyrosine kinase inhibitors such as lapatinib and PF-00299804, mammalian target of rapamycin pathway inhibitors such as everolimus, heat-shock protein 90 inhibitors such as AUY922, HER dimerization inhibitors such as pertuzumab, and antibody-chemotherapy conjugates such as trastuzumab-emtansine, could offer alternative second-line treatments when trastuzumab-based first-line therapy fails.

An UpToDate review on “Treatment protocols for colorectal cancer” (Brenner et al, 2013) does not mention the use of ado-trastuzumab or trastuzumab as a therapeutic option. Furthermore, the NCCN’s clinical practice guideline on “Colon cancer” (Version 3.2013) does not mention the use of ado-trastuzumab or trastuzumab as a therapeutic option.

Appendix

Trastuzumab Dosing

According to the FDA approved labeling of Herceptin for breast cancer, the usual dose of trastuzumab is a 4 mg/kg loading dose, followed by 2 mg/kg every week (Genentech, 2006). An alternative every 3 weeks dosing schedule for breast cancer, used in the Herceptin Adjuvant (HERA) trial, is an 8 mg/kg loading dose of trastuzumab, followed by 6 mg/kg every 3 weeks (Piccart-Gebhart et al, 2005; Smith et al, 2007).

For gastric cancer, Herceptin should be administered at an initial dose of 8 mg/kg as a 90-min intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30 to 90 mins every 3 weeks until disease progression.

Twelve months of adjuvant trastuzumab is the usual medically necessary duration for persons with HER2-positive early breast cancer (Goldhirsch et al, 2013; Pivot et al, 2013).

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

88271 - 88275 Molecular cytogenetics

88341 - 88344 Immunohistochemistry or immunocytochemistry, per specimen
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>88360 - 88361</td>
<td>Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, each antibody</td>
</tr>
<tr>
<td>88367 - 88377</td>
<td>Morphometric analysis, in situ hybridization</td>
</tr>
<tr>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td>96366</td>
<td>Each additional hour (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96401-96450</td>
<td>Chemotherapy administration</td>
</tr>
<tr>
<td>Modifier 0I</td>
<td>Her-2/neu</td>
</tr>
</tbody>
</table>

**Other HCPCS codes related to the CPB:**

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<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>G0461</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; first single or multiplex antibody stain</td>
</tr>
<tr>
<td>G0462</td>
<td>Each additional single or multiplex antibody stain (list separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>J9267</td>
<td>Injection, paclitaxel, 1 mg</td>
</tr>
</tbody>
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**Trastuzumab (Herceptin):**

**HCPCS codes covered if selection criteria are met:**

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<th>Code</th>
<th>Description</th>
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<tr>
<td>J9355</td>
<td>Trastuzumab, 10 mg</td>
</tr>
</tbody>
</table>

**Other HCPCS codes related to the CPB:**

<table>
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<th>Description</th>
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<tbody>
<tr>
<td>J9045</td>
<td>Carboplatin, [Paraplatin], 50 mg</td>
</tr>
<tr>
<td>J9264</td>
<td>Injection, paclitaxel protein-bound particles, 1 mg</td>
</tr>
<tr>
<td>J9265</td>
<td>Paclitaxel, 30 mg</td>
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</table>

**ICD-9 codes covered if selection criteria are met:**

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<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>150.0 - 150.9</td>
<td>Malignant neoplasm of esophagus [HER2 positive]</td>
</tr>
<tr>
<td>151.0 - 151.9</td>
<td>Malignant neoplasm of stomach [HER2 positive]</td>
</tr>
<tr>
<td>162.2 - 162.9</td>
<td>Malignant neoplasm of bronchus and lung [HER2 Positive non-small cell lung cancer]</td>
</tr>
<tr>
<td>174.0 - 175.9</td>
<td>Malignant neoplasm of breast [HER2 positive]</td>
</tr>
<tr>
<td>V10.3</td>
<td>Personal history of malignant neoplasm of breast [HER2 positive]</td>
</tr>
</tbody>
</table>

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>142.0 - 142.9</td>
<td>Malignant neoplasm of major salivary glands</td>
</tr>
<tr>
<td>153.0 - 153.9</td>
<td>Malignant neoplasm of colon</td>
</tr>
<tr>
<td>155.1</td>
<td>Malignant neoplasm of intrahepatic bile ducts</td>
</tr>
</tbody>
</table>
156.0 - 156.9  Malignant neoplasm of gallbladder and extrahepatic bile ducts  
157.0 - 157.9  Malignant neoplasm of pancreas  
170.0 - 170.9  Malignant neoplasm of bone and articular cartilage [osteosarcoma]  
172.0 - 172.9  Malignant melanoma of skin  
182.0  Malignant neoplasm of corpus uteri, except isthmus  
183.0  Malignant neoplasm of ovary  
184.1 - 184.4  Malignant neoplasm of vulva  
185  Malignant neoplasm of prostate  
188.0 - 188.9  Malignant neoplasm of bladder  
199.1  Other malignant neoplasm of unspecified site [unknown primary]  

Other ICD-9 codes related to the CPB:  
V58.11 - V58.12  Encounter for antineoplastic chemotherapy and immunotherapy  

**Pertuzumab (Perjeta):**  

HCPCS codes covered if selection criteria are met:  

C9292  Injection, pertuzumab, 10 mg [only covered when used in combination with Trastuzumab for recurrent or metastatic HER2-positive breast cancer]  
J9306  Injection, pertuzumab, 1 mg  

ICD-9 codes covered if selection criteria are met:  

174.0 - 175.9  Malignant neoplasm of breast [HER2 positive]  

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):  

151.0 - 151.9  Malignant neoplasm of stomach  
153.0 - 153.9  Malignant neoplasm of colon  
154.0 - 154.8  Malignant neoplasm of rectum, rectosigmoid junction, and anus  
155.1  Malignant neoplasm of intrahepatic bile ducts  
156.0 - 156.9  Malignant neoplasm of gallbladder and extrahepatic bile ducts  
162.2 - 162.9  Malignant neoplasm of bronchus and lung  
182.0  Malignant neoplasm of corpus uteri, except isthmus  
183.0  Malignant neoplasm of ovary  
184.1 - 184.4  Malignant neoplasm of vulva  
185  Malignant neoplasm of prostate  
188.0 - 188.9  Malignant neoplasm of bladder
Translumab (Herceptin), Ado-Trastuzumab (Kadcyla) and Pertuzumab (Perjeta)

**ado-trastuzumab emtansine (Kadcyla):**

**HCPCS codes covered if selection criteria are met:**

- J9354 Injection, ado-trastuzumab emtansine, 1 mg

**Other HCPCS codes related to the CPB:**

- J9171 Injection, docetaxel, 1 mg
- J9265 Injection, paclitaxel, 30 mg
- J9355 Trastuzumab, 10 mg

**ICD-9 codes covered if selection criteria are met:**

- 174.0 - 175.9 Malignant neoplasm of breast [HER2-positive previously treated with trastuzumab]

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

- 151.0 - 151.9 Malignant neoplasm of stomach
- 153.0 - 154.9 Malignant neoplasm of colon, rectum, rectosigmoid junction and anus
- 155.1 Malignant neoplasm of intrahepatic bile ducts
- 156.0 - 156.9 Malignant neoplasm of gallbladder and extrahepatic bile ducts

The above policy is based on the following references:

**Trastuzumab (Herceptin):**


61. Gosselin C, Dagenais P. Diagnostic performance of techniques used for HER-2 testing in breast cancer [summary]. AETMIS 08-03. Montreal, QC: Agence
d’Evaluation des Technologies et des Modes d’Intervention en Sante (AETMIS); May 2008.


74. Clark JW, Grothey A. Systemic chemotherapy for nonoperable metastatic colorectal cancer: Treatment recommendations. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2012.


86. Leitao MM, Zivanovic O. Small cell neuroendocrine carcinoma of the cervix. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2015.


Pertuzumab (Perjeta):


Ado-Trastuzumab Emtansine (Kadcyla):
