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PHARMACY / MEDICAL POLICY – 5.01.514

HER2 Inhibitors

BCBSA Ref. Policy: 5.01.12

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Clicking this icon returns you to the hyperlinks menu above.

Introduction

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

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

Policy Coverage Criteria

Drug	Medical Necessity
Oral Drugs	
Generic lapatinib	**Generic lapatinib may be considered medically necessary for the treatment of HER2-positive breast cancer:** • In combination with capecitabine for individuals with advanced or metastatic disease who received prior therapy including an anthracycline, a taxane, and trastuzumab and progressed on trastuzumab **OR** • In combination with letrozole for postmenopausal individuals with hormone receptor-positive, metastatic disease that overexpresses the HER2 receptor for whom hormonal therapy is indicated **AND** • The dose prescribed is less than or equal to 1,500 mg per day
Tykerb (lapatinib)	**Tykerb (lapatinib) may be considered medically necessary for the treatment of HER2-positive breast cancer:** • In combination with capecitabine for individuals with advanced or metastatic disease who received prior therapy including an anthracycline, a taxane, and trastuzumab and progressed on trastuzumab **OR** • In combination with letrozole for postmenopausal individuals with hormone receptor-positive, metastatic disease that overexpresses the HER2 receptor for whom hormonal therapy is indicated **AND** • The individual has tried generic lapatinib first and had an inadequate response or intolerance to generic lapatinib **AND** • The dose prescribed is less than or equal to 1,500 mg per day
Nerlynx (neratinib)	**Nerlynx (neratinib) may be considered medically necessary for use as extended adjuvant treatment in HER2-positive breast cancer when all the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity
	• Has a diagnosis of stage III or lower breast cancer that overexpresses or has amplified HER2 protein **AND** • Nerlynx is used as adjuvant therapy **AND** • Is used following adjuvant trastuzumab-based therapy **AND** • The dose is limited to 240 mg (six tablets) per day **AND** • The total duration of therapy will be limited to a maximum of 1 year when used for extended adjuvant treatment **Nerlynx (neratinib) may be considered medically necessary for use in advanced or metastatic HER2-positive breast cancer when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a diagnosis of stage III or IV breast cancer that overexpresses or has amplified HER2 protein **AND** • Has received two or more prior anti-HER2 based regimens in the metastatic setting (stage IV) **AND** • Nerlynx is used in combination with capecitabine **AND** • The dose is limited to 240 mg (six tablets) per day
Tukysa (tucatinib)	**Tukysa (tucatinib) may be considered medically necessary for the treatment of advanced unresectable or metastatic HER2-positive breast cancer, including individuals with brain metastases, when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has received one or more prior anti-HER2-based regimens in the metastatic setting **AND** • Tukysa (tucatinib) is being used in combination with trastuzumab and capecitabine

Drug	Medical Necessity
	AND • The dose is limited to 600 mg per day (taken as 300 mg twice daily) **Tukysa (tucatinib) may be considered medically necessary for the treatment of unresectable or metastatic colorectal cancer when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a diagnosis of unresectable or metastatic colorectal cancer that is RAS wild-type, HER2-positive (3+ by immunohistochemistry (IHC) OR 2+ by IHC with overexpression by fluorescence in situ hybridization (FISH) or amplification by next generation sequencing (NGS) testing) **AND** • Disease has progressed following the treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy **AND** • Tukysa is in combination with trastuzumab **AND** • The dose is limited to 600 mg per day (taken as 300 mg twice daily)
Injectable Drugs	
First-line: • **Kanjinti (trastuzumab-anns)** • **Trazimera (trastuzumab-qyyp)**	**Kanjinti (trastuzumab-anns) OR Trazimera (trastuzumab-qyyp) may be considered medically necessary for the treatment of individuals with HER2-positive breast cancer. This includes use as adjuvant therapy, neoadjuvant therapy, and treatment of metastatic disease:** • For adjuvant treatment of HER2-positive breast cancer (node positive or negative) as part of several different combination therapy regimens or as a single agent following prior chemotherapy **OR** • For treatment of HER2-positive metastatic breast cancer in combination therapy or as a single agent

Drug	Medical Necessity
	Kanjinti (trastuzumab-anns) OR Trazimera (trastuzumab-qyyp) may be considered medically necessary for the treatment of unresectable or metastatic colorectal cancer when ALL the following criteria are met: • The individual is aged 18 years or older **AND** • Has a diagnosis of unresectable or metastatic colorectal cancer that is RAS wild-type, HER2-positive (3+ by immunohistochemistry (IHC) OR 2+ by IHC with overexpression by fluorescence in situ hybridization (FISH) or amplification by next generation sequencing (NGS) testing) **AND** • Disease has progressed following the treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy **AND** • Is used in combination with Tukysa (tucatinib) **Kanjinti (trastuzumab-anns) OR Trazimera (trastuzumab-qyyp) may be considered medically necessary for the treatment of metastatic gastric cancer or gastroesophageal junction adenocarcinoma when all the following are met:** • The individual has tumors that overexpress the HER2 protein (HER2-positive) **AND** • Used in combination with platinum-based agents (e.g., cisplatin, carboplatin, oxaliplatin) AND capecitabine or 5-fluorouracil for palliative treatment **Note**: Kanjinti (trastuzumab-anns) and Trazimera (trastuzumab-qyyp) are biosimilars to Herceptin (trastuzumab) and are administered as an IV infusion. **Note:** Kanjinti and Trazimera are not recommended for use with anthracyclines in palliative therapy for metastatic gastric cancer or gastroesophageal junction adenocarcinoma.

Drug	Medical Necessity
Herceptin Hylecta (trastuzumab and hyaluronidase-oysk)	**Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) may be considered medically necessary for the treatment of individuals with HER2-positive breast cancer. This includes use as adjuvant therapy, neoadjuvant therapy, and treatment of metastatic disease:** • For adjuvant treatment of HER2-positive breast cancer (node positive or negative) as part of several different combination therapy regimens or as a single agent following prior chemotherapy **OR** • For treatment of HER2-positive metastatic breast cancer in combination therapy or as a single agent **AND** • The individual has had an inadequate response or intolerance to Kanjinti (trastuzumab-anns) OR Trazimera (trastuzumab-qyyp) ○ **Exception:** This may be granted when documentation is provided of difficult venous access. **Note:** Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) is administered subcutaneously and should be administered by a healthcare professional.
Second-line: • **Herceptin (trastuzumab)** • **Hercessi (trastuzumab-strf)** • **Herzuma (trastuzumab-pkrb)** • **Ogivri (trastuzumab-dkst)** • **Ontruzant (trastuzumab-dttb)**	**Herceptin (trastuzumab), Hercessi (trastuzumab-strf), Herzuma (trastuzumab-pkrb), Ogivri (trastuzumab-dkst), and Ontruzant (trastuzumab-dttb) may be considered medically necessary for the treatment of individuals with HER2-positive breast cancer after adequate trial and failure of Kanjinti OR Trazimera. This includes use as adjuvant therapy, neoadjuvant therapy, OR treatment of metastatic disease.** • For adjuvant treatment of HER2-positive breast cancer (node positive or negative) as part of several different combination therapy regimens or as a single agent following prior chemotherapy **OR** • For treatment of HER2-positive metastatic breast cancer in combination therapy or as a single agent **AND**

Drug	Medical Necessity
	• The individual has had an inadequate response or intolerance to Kanjinti (trastuzumab-anns) OR Trazimera (trastuzumab-qyyp) **Herceptin (trastuzumab), Hercessi (trastuzumab-strf), Herzuma (trastuzumab-pkrb), Ogivri (trastuzumab-dkst), and Ontruzant (trastuzumab-dttb) may be considered medically necessary for the treatment of unresectable or metastatic colorectal cancer when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a diagnosis of unresectable or metastatic colorectal cancer that is RAS wild-type, HER2-positive (3+ by immunohistochemistry (IHC) OR 2+ by IHC with overexpression by fluorescence in situ hybridization (FISH) or amplification by next generation sequencing (NGS) testing) **AND** • Disease has progressed following the treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy **AND** • Is used in combination with Tukysa (tucatinib) **AND** • Has had an inadequate response or intolerance to Kanjinti (trastuzumab-anns) OR Trazimera (trastuzumab-qyyp) **Herceptin (trastuzumab), Hercessi (trastuzumab-strf), Herzuma (trastuzumab-pkrb), Ogivri (trastuzumab-dkst), and Ontruzant (trastuzumab-dttb) may be considered medically necessary for the treatment of metastatic gastric cancer or gastroesophageal junction adenocarcinoma when all the following are met:** • The individual has tumors that overexpress the HER2 protein (HER2-positive) **AND**

Drug	Medical Necessity
	• Has received an adequate trial and failure of Kanjinti OR Trazimera used in combination with platinum-based agents (e.g. cisplatin, carboplatin, oxaliplatin) and capecitabine or 5-fluorouracil for palliative treatment **Note:** Hercessi (trastuzumab-strf), Herzuma (trastuzumab-pkrb), Ogivri (trastuzumab-dkst), and Ontruzant (trastuzumab-dttb) are biosimilars to Herceptin (trastuzumab) and are administered as an IV infusion. **Note:** Herceptin, Hercessi, Herzuma, Ogivri, and Ontruzant are not recommended for use with anthracyclines in palliative therapy for metastatic gastric cancer or gastroesophageal junction adenocarcinoma.
Perjeta (pertuzumab)	**Perjeta (pertuzumab) may be considered medically necessary for the treatment of previously untreated HER2-positive breast cancer or recurrent breast cancer when all the following are met:** • Perjeta (pertuzumab) will be used after adjuvant therapy **AND** • Perjeta (pertuzumab) will be used combination with trastuzumab as adjuvant therapy, neoadjuvant therapy, or for the treatment of metastatic disease **AND** • Perjeta (pertuzumab) will be used in combination with docetaxel or paclitaxel as adjuvant therapy, neoadjuvant therapy, or for the treatment of metastatic disease **Perjeta (pertuzumab) may be considered medically necessary when used in combination with trastuzumab and chemotherapy as:** • Neoadjuvant treatment of individuals with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer as part of a complete treatment regimen for early breast cancer **OR** • Adjuvant treatment of individuals with HER2-positive early breast cancer. **Note:** Perjeta (pertuzumab) can be used in combination with Herceptin (trastuzumab) or Herceptin Hylecta (trastuzumab and hyaluronidase-

Drug	Medical Necessity
	oysk). Perjeta (pertuzumab) can also be used in combination with the biosimilars Hercessi (trastuzumab-strf), Herzuma (trastuzumab-pkrb), Kanjinti (trastuzumab-anns), Ogivri (trastuzumab-dkst), Ontruzant (trastuzumab-dttb) and Trazimera (trastuzumab-qyyp).
Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) SC	**Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) may be considered medically necessary for the treatment of previously untreated HER2-positive breast cancer or recurrent breast cancer after adjuvant therapy when all the following are met:** • Used in combination with docetaxel or paclitaxel as adjuvant therapy, neoadjuvant therapy, or treatment of metastatic disease **Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) may be considered medically necessary when used in combination with chemotherapy as:** • Neoadjuvant treatment of individuals with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer as part of a complete treatment regimen for early breast cancer **OR** • Adjuvant treatment of individuals with HER2-positive early breast cancer. **Note:** Switching therapy from Perjeta (pertuzumab) and/or a trastuzumab product to Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) during treatment is allowed.
Kadcyla (ado-trastuzumab emtansine)	**Kadcyla (ado-trastuzumab emtansine) may be considered medically necessary as a single agent when used for:** • The treatment of individuals with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane separately or in combination **AND** • The individual has received prior treatment for metastatic disease **OR** • Developed recurrent disease during or within 6 months of completing adjuvant therapy

Drug	Medical Necessity
	Kadcyla (ado-trastuzumab emtansine) may be considered medically necessary for the treatment of HER2-positive early breast cancer when all the following are met: • Kadcyla (ado-trastuzumab emtansine) will be used as an adjuvant treatment **AND** • The individual has residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment
Enhertu (fam-trastuzumab deruxtecan-nxki)	**Enhertu (fam-trastuzumab deruxtecan-nxki) may be considered medically necessary for the treatment of adult individuals with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:** • In the metastatic setting **OR** • In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy **Enhertu (fam-trastuzumab deruxtecan-nxki) may be considered medically necessary for the treatment of adult individuals with unresectable or metastatic hormone receptor (HR)-positive HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer when the following is met:** • The cancer progressed on one or more endocrine therapies (e.g., anastrozole, exemestane, letrozole, tamoxifen) in the metastatic setting **Enhertu (fam-trastuzumab deruxtecan-nxki) may be considered medically necessary for the treatment of adult individuals with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who:** • Have received a prior chemotherapy in the metastatic setting **OR**

Drug	Medical Necessity
	• Developed disease recurrence during or within six months of completing adjuvant chemotherapy **Enhertu (fam-trastuzumab deruxtecan-nxki) may be considered medically necessary for the treatment of adult individuals with unresectable or metastatic non-small cell cancer (NSCLC) who:** • Have activating HER2 (ERBB2) mutations **AND** • Have received a prior systemic therapy **Enhertu (fam-trastuzumab deruxtecan-nxki) may be considered medically necessary for the treatment of HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma when all the following are met:** • The individual is aged 18 years or older **AND** • Has locally advanced or metastatic disease **AND** • Has received a prior trastuzumab-based regimen **Enhertu (fam-trastuzumab deruxtecan-nxki) may be considered medically necessary for the treatment of HER2-positive (IHC 3+) solid tumors when all the following are met:** • The individual is aged 18 years or older **AND** • Has unresectable or metastatic disease **AND** • Has received a prior systemic treatment **AND** • Has no satisfactory alternative treatment options **Note**: HER2-low breast cancer is diagnosed based on immunohistochemistry (IHC) analysis and sometimes by in-situ hybridization (ISH) analysis. HER2-low breast

Drug	Medical Necessity
	cancer has a 1+ score on an IHC test or a 2+ score on an IHC test plus a negative ISH test.
Margenza (margetuximab-cmkb)	**Margenza (margetuximab-cmkb) may be considered medically necessary for the treatment of metastatic HER2-positive breast cancer when all the following are met:** • The individual is aged 18 years or older **AND** • Has received two or more prior anti-HER2 regimens AND at least one of which was for metastatic disease **AND** • Margenza (margetuximab-cmkb) will be used in combination with chemotherapy

Drug	Investigational
As listed	**All other uses of the medications listed in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for the drugs listed in this policy may be approved up to 12 months.** **All other reviews for the oral drugs listed in policy may be approved up to 3 months.** **All other reviews for the injectable drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews of oral and injectable drugs may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart**

Length of Approval	
Approval	**Criteria**
	notes demonstrate that the individual continues to show a positive clinical response to therapy.

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
J3590	Unclassified biologics (use to report: Hercessi)
J9306	Injection, pertuzumab (Perjeta), 1 mg
J9316	Injection, pertuzumab, trastuzumab, and hyaluronidase-zzxf, (Phesgo) per 10 mg
J9353	Injection, margetuximab-cmkb, (Margenza) 5 mg
J9354	Injection, ado-trastuzumab emtansine (Kadcyla), 1 mg
J9355	Injection, trastuzumab, excludes biosimilar, (Herceptin) 10 mg
J9356	Injection, trastuzumab, (Herceptin Hylecta) 10mg and hyaluronidase-oysk
J9358	Injection, fam-trastuzumab deruxtecan-nxki (Enhertu), 1 mg
Q5112	Injection, trastuzumab-dttb, biosimilar, (Ontruzant), 10 mg
Q5113	Injection, trastuzumab-pkrk, biosimilar, (Herzuma), 10 mg
Q5114	Injection, trastuzumab-dkst, biosimilar, (Ogivri), 10 mg
Q5116	Injection, trastuzumab-qyyp, biosimilar, (Trazimera), 10 mg
Q5117	Injection, trastuzumab-anns, biosimilar, (Kanjinti), 10 mg
Q5146	Injection, trastuzumab-strf (hercessi), biosimilar, 10 mg (new code effective 01/01/25)

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

Related Information

HER2 Testing

Appropriate individual selection for trastuzumab therapy is predicated on detection of HER2 overexpression. HER2 overexpression should be assessed only by facilities with demonstrated proficiency in the specific assay being used. Unreliable results may result from improper assay performance. Several assays are commercially available to aid selection of individuals for trastuzumab therapy. These include the HercepTest and Pathway HER2/neu, which are immunohistochemical assays (IHC), and PathVysion and HER2 FISH pharmDx, which are fluorescence in situ hybridization assays (FISH).

Cardiac Monitoring

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

Unresolved Issues

RCTs have consistently reported a beneficial effect of adjuvant trastuzumab in combination with adjuvant chemotherapy in individuals with completely resected HER2-positive breast cancer. However, these trials have not resolved the issues of initiating trastuzumab before or after adjuvant chemotherapy or taking trastuzumab as concurrent or sequential therapy.

Duration of Therapy

Updated results from the HERA trial indicated that 2 years of adjuvant trastuzumab was not more effective than 1 year of treatment but was associated with more adverse events. The PHARE trial supported 1 year of trastuzumab rather than 6 months of treatment. A 2012 Cochrane meta-analysis also supported the use of 1 year of trastuzumab treatment given with adjuvant chemotherapy rather than for shorter periods.

Starting Trastuzumab After Completing Adjuvant Chemotherapy

Trastuzumab has been rapidly integrated into the adjuvant therapy of individuals with HER2-positive early-stage breast cancer. When the interim results were reported in 2005, there was interest in offering trastuzumab to individuals who would otherwise meet criteria, but who had already completed adjuvant therapy. This group of individuals still has not been studied formally. Individuals in the HERA trial started trastuzumab a median of 8 months after diagnosis and 3 months after completing all chemotherapy.

Concurrent Versus Sequential Therapy

At present, 1 prospective observational study has assessed the optimal regimen of trastuzumab within the overall regimen of adjuvant therapy, specifically whether concurrent or sequential trastuzumab is the preferred course. Six-year interim results of the NCCTG N9831 trial have demonstrated longer DFS with concurrent trastuzumab (with paclitaxel) than with sequential trastuzumab.

Safety Concerns with Ado-Trastuzumab Emtansine

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

- Ado-trastuzumab emtansine is associated with known gestational adverse effects, and should not be used in pregnant women. Effective contraception should be used during and for at least 6 months following treatment.
- Increases in liver function enzymes are common. Dose modifications based on liver function tests are recommended.

- Decreases in left ventricular ejection fraction have been noted. Inclusion criteria for the EMILIA trial included a LV ejection fraction of at least 50% or greater
- The safety and efficacy of ado-trastuzumab emtansine in pediatric individuals has not been established
- Other safety concerns, which generally do not warrant a change in management, include infusion reactions, pulmonary toxicity, GI symptoms, and fatigue

Benefit Application

State and federal mandates requiring coverage of FDA-approved drugs may supersede this policy.

Evidence Review

Description

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

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

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

Herceptin (trastuzumab) in Breast Cancer

Metastatic

The initial 1998 approval by the FDA for trastuzumab in metastatic breast cancer was based on results from 2 pivotal clinical trials. In one trial, single-agent trastuzumab was given to women (n=222) who had received 1 or 2 courses of cytotoxic chemotherapy, yielding an objective response rate (ORR) of 15% and a median duration of response of 9.1 months.[1] In a second randomized trial (n=469), trastuzumab was evaluated as part of a first-line combination regimen consisting of either doxorubicin (A) plus cyclophosphamide (C) or paclitaxel (P).[2] The addition of trastuzumab to chemotherapy resulted in an increased response rate (50% vs. 32%, $p<0.001$), longer median response duration (9.1 vs. 6.1 months, $p<0.001$), and prolonged overall survival (OS) (25.1 months vs. 20.3, $p=0.046$) compared to chemotherapy alone. Because a significantly higher incidence of New York Heart Association (NYHA) class III or IV cardiotoxicity was reported in this trial among individuals who received AC plus trastuzumab, compared to AC, paclitaxel/trastuzumab, or paclitaxel, the FDA and others subsequently cautioned against using a regimen that combined trastuzumab with doxorubicin.[3,4]

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

Kaufman and colleagues reported the results of the first randomized Phase III trial combining a hormonal agent (aromatase inhibitor anastrozole) and trastuzumab without chemotherapy.[8] Individuals were postmenopausal with HER2 and hormone receptor-positive metastatic disease (individuals with CNS metastases were excluded). Individuals were randomized to receive trastuzumab plus anastrozole (n=103) or anastrozole alone (n=104). Baseline characteristics were balanced between the two groups. The primary endpoint was progression free survival (PFS), defined as the time from randomization and the date of disease progression or death. There were a total of 187 withdrawals from the trial treatment, most frequently due to progressive disease. In the anastrozole-only arm, 70% of the individuals who experienced progressive disease subsequently crossed over to receive a trastuzumab containing regimen. Progression free survival was significantly improved in the trastuzumab plus anastrozole arm with a median PFS of 4.8 months (95% confidence interval [CI]: 3.7 to 7.0 months) versus 2.4

months (95% CI: 2.0 to 4.6 months) in the anastrozole-only arm (hazard ration [HR] =0.63; 95%CI: 0.47-0.84; p=0.0016). Grade 3 and 4 adverse events were 23% and 5%, respectively, in the trastuzumab plus anastrozole arm, and 15% and 1% in the anastrozole-only arm.

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

Adjuvant

Results from randomized trials provide data on clinical outcomes of adjuvant trastuzumab therapy: the Breast Cancer International Research Group 006 trial (BCIRG 006, n=3,222)[10]; the Herceptin Adjuvant Trial (HERA, n=5,090)[11]; the North Central Cancer Treatment Group N9831 trial (NCCTG N9831, n=3,505)[12]; the North American National Surgical Adjuvant Breast and Bowel Project B31 trial (NSABP B31, n=2,030)[13]; and, the Finnish Herceptin Study (FinHer, n=232)[14]. All women enrolled in these studies tested positive for HER2 using either immunohistochemical assays (IHC) or fluorescence in situ hybridization assays (FISH) assays. There were important differences in individual characteristics, trial design, and implementation, as reviewed in depth elsewhere.[7,15-18] **Table 1** summarizes the design and results of those trials.

Table 1. Randomized Trials on Clinical Outcomes of Adjuvant Trastuzumab Therapy

Trial (ref)	Tumor Characteristics	Design	Trastuzumab Schedule	F/U (Median, Years)	DFS HR vs. Controls [95% CI] (p)	OS HR vs. Controls [95% CI] (p)
BCIRG[10]	node-positive, or high-risk node-negative	AC→D AC→DH DCH	Q1wk w/CTx Q3wk postCTx	3	AC→DH: 0.61 [0.48-0.76] (< 0.0001) DCH: 0.67 [0.54-0.83] (0.0003)	AC→DH: 0.59 [0.42-0.85] (0.004) DCH: 0.66 [0.47-0.93] (0.017)
HERA[11]	node-positive, or node-negative with tumor ≥1 cm	Accepted CTx CTx→H (1 yr) CTx→H (2 yrs)	Q3wk postCTx	2	0.64 [0.43-0.57] (<0.0001)	0.66 [0.47-1.23] 0.0115)
NCCTG N9831[12]	node-positive, or if node-negative, with primary tumor >1 cm if ER/PR-negative, or >2 cm if ER/PR-positive	AC→P AC→P→H AC→PH	Q1wk w/CTx Q1wk postCTx	2	combined data: 0.48 [0.39-0.59] (<0.0001)	combined data: 0.67 [0.48-0.93] (0.015)
NSABP B31[13]	node-positive	AC→P AC→PH	Q1wk w/CTx Q1wk postCTx	2		
FinHer[14]	node-positive, or node-negative and ≥2 cm and PR-negative	D or V→FEC DH or VH→FEC	Q1wk w/CTx	3	0.42 [0.21-0.83] (0.01)	0.41 [0.16-1.08] (0.07)

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

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

Grade III/IV congestive heart failure (CHF) or cardiac-related death for individuals receiving trastuzumab-containing adjuvant regimens ranged from 0 (FinHer) to 4.1% (NSABP B31) overall, with age and baseline left-ventricular ejection fraction related to the risk for cardiac dysfunction. Concurrent use of trastuzumab and a taxane following 4 cycles of AC resulted in the highest rates of CHF (1.5%, 2.4%, and 3.4% for the BCIRG, N9831, and B31 trials, respectively). Sequential administration of anthracyclines, taxanes, and trastuzumab resulted in CHF rates of 1.4% and 0.5% for the N9831 and HERA trials, respectively. The non-anthracycline arm of the BCIRG trial had the lowest rate (0.3%) of CHF. While the acceptable rate of cardiac events overall was likely related to rigorous monitoring during the trials, cross-trial comparisons and conclusions are difficult due to differences in definitions of cardiac events, evaluations for cardiac safety, analysis of cardiac endpoints (cumulative vs. overall incidence) and duration of follow-up.

Neoadjuvant

A randomized, controlled trial has been published on the benefits of adding trastuzumab to neoadjuvant chemotherapy.[19] The study sequentially administered two neoadjuvant chemotherapy regimens followed by surgery to breast cancer individuals with stage II to IIIA disease and compared paclitaxel (four 3-week cycles) followed by fluorouracil, epirubicin, and cyclophosphamide (FEC; four 3-week cycles) with versus without trastuzumab. A data monitoring committee ended the trial after investigators randomized 42 individuals, when a

requested (but unplanned) analysis showed pathologic complete response (pCR) rates of 25% in the arm without and 66.7% in the arm with trastuzumab. Approximately the same proportion of individuals in each arm (52.6% without and 56.5% with trastuzumab) received breast-conserving surgery, but individual choice likely influenced these results. A subsequent report of the same study included longer follow-up for randomized individuals, and additional nonrandomized individuals.[20] Results showed pCR in 26.3% (95% CI: 9–51%) of 19 individuals randomized to neoadjuvant chemotherapy without trastuzumab, 65.2% (95% CI: 43–84%) of 23 individuals randomized to the same neoadjuvant regimen plus trastuzumab, and 54.5% (95% CI: 32.2–75.6%) of 22 consecutive nonrandomized individuals also given the same regimen plus trastuzumab.[20] At a median follow-up of 36.1 months for randomized individuals, 3 in the chemotherapy-only arm experienced recurrence (1 of whom died), and none in the arm with added trastuzumab.

Although few recurrences or deaths have occurred thus far in this terminated randomized, controlled trial, the 2-fold increase in pCR rate is unlikely to be a chance result.[19,20] Analyses from randomized, controlled trials[21-23] and single-arm studies[24-26] showed that individuals with pCR after neoadjuvant chemotherapy (determined postoperatively) had significantly longer overall, disease-free, and/or recurrence-free survival than those who did not achieve pCR. This also was true when those who achieved pCR were compared with those who achieved clinically complete responses but were subsequently shown by postoperative pathology to have residual (microscopic) invasive disease. Thus, improving pCR rate by adding trastuzumab to neoadjuvant chemotherapy for HER2 individuals with high-risk, larger tumors predicts improved overall and disease-free survival.

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

Herceptin (trastuzumab) in Non-Breast Cancer

Gastric Cancer

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

Van Cutsem and colleagues reported the results of a Phase III, open-label, randomized, multicenter (122 centers in 24 countries) trial in which individuals with HER2-positive, locally advanced, recurrent, or metastatic gastroesophageal or gastric adenocarcinoma received chemotherapy consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin with or without trastuzumab.[28] Individuals who received the trastuzumab were given it every three weeks for 6 cycles, until disease progression. The primary endpoint of the study was overall survival; secondary endpoints were overall response rate (ORR), PFS, time to progression, duration of response and safety. Median follow-up was 18.6 months in the chemotherapy plus trastuzumab group and 17.1 months in the chemotherapy-alone group. Tumors from 3,807 individuals were tested for HER2 status; 22.1% were positive. Five-hundred ninety-four individuals were randomized to the 2 treatment arms. Median OS for the group that received trastuzumab compared to those that did not was 13.8 months (95% CI: 12-16) versus 11.1 months (95% CI: 10-13) (p=0.0046; HR 0.74; 95%CI 0.60-0.91). ORR was 47.3% for those that received trastuzumab versus 34.5% for those that did not (p=0.0017). Rates of overall grade 3 or 4 adverse events (201 [68%] versus 198 [68%]) and cardiac adverse events (17 [6%] versus 18 [6%]) did not differ between the chemotherapy and trastuzumab versus chemotherapy alone groups.

Prostate Cancer

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

Salivary Gland Cancer

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

Ovarian and Peritoneal Cancer

A study of trastuzumab in individuals with recurrent or refractory ovarian or primary peritoneal carcinoma found a low rate of clinical response to treatment.[34]

Non-Small Cell Lung Cancer

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

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

Esophageal Cancer

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

Bladder and Kidney Cancer

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

Summary

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

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

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

Tykerb (lapatinib)

The efficacy and safety of Tykerb (lapatinib) in combination with capecitabine in breast cancer were evaluated in a randomized, Phase III trial. Individuals eligible for enrollment had HER2

(ErbB2) over-expressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab.

Individuals were randomized to receive either lapatinib 1,250 mg once daily (continuously) plus capecitabine 2,000 mg/m2/day on Days 1-14 every 21 days, or to receive capecitabine alone at a dose of 2,500 mg/m2/day on Days 1-14 every 21 days. The endpoint was time to progression (TTP). TTP was defined as time from randomization to tumor progression or death related to breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was discontinued. Three hundred ninety-nine (399) individuals were enrolled in this study. The median age was 53 years and 14% were older than 65 years. Ninety-one percent (91%) were Caucasian. Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of individuals had prior treatment with anthracyclines, taxanes, and trastuzumab. Independent assessment of individuals showed a median time to progression of 27.1 weeks in the lapatinib group vs. 18.6 weeks in controls. Response rates were 23.7% (95% CI 18.0-30.3) and 13.9% (95% CI 9.5-19.5), respectively (HR 0.57, 95% CI 0.43-0.77, p=0.00013).

Kadcyla (ado-trastuzumab emtansine)

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

Randomized, Controlled Trial

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

Potential bias introduced by the open-label trial design was minimized by assessor blinding of PFS and tumor response endpoints and using an easily measured endpoint, OS.

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

Uncontrolled Trials

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

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

Nerlynx (neratinib)

In the multicenter, randomized, double-blind, placebo-controlled phase-3 ExteNET, the efficacy of 12 months of neratinib were evaluated in stage 1-3 HER-2 positive breast cancer. Individuals

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

Other HER2 Inhibitors

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

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

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

Kadcyla (ado-trastuzumab emtansine), also known as trastuzumab-DM1 or T-DM1, is an antibody-drug conjugate comprising trastuzumab and emtansine (DM1). It is a HER2 antagonist that is intended as treatment for individuals with breast cancers that overexpress HER2, and it may also have applications for other HER-2 positive malignancies. Emtansine (previously called "DM1" for "derivative of maytansine 1") is a sulfur-containing derivative of the potent microtubule inhibitor, maytansine. Emtansine is conjugated to trastuzumab by lysine side chains, forming a stable thioether linkage. T-DM1 binds HER2 with an affinity comparable to that of trastuzumab. Once internalized, proteolytic degradation of the linker releases both trastuzumab and the active metabolite, maleimidomethyl cyclohexane-1-carboxylate (MCC)-emtansine. MCC-emtansine contains both positive and negative charges and therefore does not readily cross

plasma membranes, maintaining intracellular concentrations. Ado-trastuzumab emtansine has been shown to preserve the antitumor activity of trastuzumab (described above). Death of HER2-expressing cells therefore results from effects of both active moieties of ado-trastuzumab emtansine.

Tukysa (tucatinib)

Tukysa is an oral, small-molecule tyrosine kinase inhibitor (TKI) of HER2. Tukysa, in combination with trastuzumab, is indicated for the treatment of adult individuals with RAS wild-type HER2-positive unresectable or metastatic colorectal cancer that has progressed following the treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. This accelerated approval was granted based on the assessment of the tumor response rate and durability of the response. Trastuzumab works by inhibiting the HER2-mediated signaling pathway, which prevents HER2 homodimerization. Additionally, trastuzumab acts as a mediator of antibody-dependent cellular cytotoxicity.

The effectiveness of the combination of Tukysa and trastuzumab was evaluated in phase 2, open-label, multicenter clinical trial that included 84 individuals with RAS wild-type, HER2-positive, unresectable, or metastatic colorectal cancer who had prior treatment with fluoropyrimidines, oxaliplatin, irinotecan-based chemotherapy. All the individuals received Tukysa 300 mg orally twice a day along with a loading dose of trastuzumab. The treatment continued until disease progression or unacceptable toxicity. The primary efficacy endpoints were overall response rate (ORR) and duration of response (DOR). The study result showed an overall response rate of 38%, with 3% of individuals achieving a complete response. Of the 32 individuals evaluated for response duration, 81% individuals had duration of response of at least 6 months and 34% individuals had duration of response that lasted for at least 12 months.

2012 Update

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

2013 Update

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

2014 Update

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

2015 Update

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

2018 Update

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

2019 Update

Reviewed all FDA-approved indications for drugs in policy and made an additional update to Tykerb criteria to clarify Tykerb is to be used in combination with capecitabine for the treatment of HER2-positive breast cancer patients in patients with advanced or metastatic disease.

2020 Update

Reviewed all FDA-approved indications for drugs in policy and no new information was identified that required changes to policy statements. Updated Evidence Review section of policy removing outdated NCCN recommendations.

2021 Update

Reviewed prescribing information for all drugs in policy. No new information was identified that would require changes to the medical policy criteria. Updated information for the following sections: unresolved issues, duration of therapy, starting trastuzumab after completing adjuvant chemotherapy, and concurrent versus sequential therapy.

2022 Update

Reviewed prescribing information for all drugs in policy. Updated the Enhertu (fam-trastuzumab deruxtecan-nxki) indication for the treatment of metastatic breast cancer and added coverage for use in the neoadjuvant or adjuvant setting. Enhertu is now approved for earlier use in HER2-positive breast cancer treatment moving up from the third-line setting to second-line. This expanded approval for breast cancer was based on the Phase 3 DESTINY-Breast03 trial in which Enhertu reduced the risk of disease progression or death by 72% versus Kadcyla (ado-trastuzumab emtansine). Enhertu is also approved for use in HER2-low breast cancer as a second-line agent. This was based on the DESTINY-Breast04 trial, which showed a median overall survival of 23.4 months with Enhertu compared to 16.8 months with usual chemotherapy. In addition, Enhertu is now approved for use in non-small cell lung cancer. This accelerated approval was supported by the DESTINY-Lung02 trial; an interim efficacy analysis showed an overall response rate of 58% in patients whose tumors have an activating HER2 mutation. Added coverage for Enhertu (fam-trastuzumab deruxtecan-nxki) for adults with unresectable or metastatic HER2-low breast cancer and unresectable or metastatic non-small cell lung cancer. Added to Herzuma (trastuzumab-pkrb) coverage for the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

2023 Update

Reviewed prescribing information for all drugs in policy. Updated coverage criteria for Tukysa when used in combination with trastuzumab for adult individuals with RAS wild-type, HER2-positive unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy. Removed Brand name trademarks throughout the policy for the process of standardization. Effective January 1, 2024, following 90-day provider notification due to changes in the preferred medical benefit drugs: Moved Trazimera to second-line (non-preferred) agent.

2024 Update

Reviewed prescribing information for all drugs in policy. Minor correction made to add the quantity limit requirement for Tukysa (tucatinib) to the colorectal cancer coverage criteria. Updated Enhertu (fam-trastuzumab deruxtecan-nxki) coverage criteria to include treatment of certain individuals with an unresectable or metastatic solid tumor. Added Hercessi (trastuzumab-strf) as a second line trastuzumab product.

2025 Update

Reviewed prescribing information for all drugs in policy. Added a new indication to Enhertu (fam-trastuzumab deruxtecan-nxki) for the treatment of adult individuals with HR-positive HER2-low or HER2-ultralow breast cancer that has progressed on one or more endocrine therapies in the metastatic setting. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

Regulatory Status

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

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

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

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

The following biosimilars have been approved by the FDA for trastuzumab for the treatment of HER2-overexpressing breast cancer and/or HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

- April 2024, Hercessi (trastuzumab-strf; Accord BioPharma Inc.)
- June 2019, Kanjinti (trastuzumab-anns; Amgen)
- March 2019, Trazimera (trastuzumab-qyyp; Pfizer)
- January 2019, Ontruzant (trastuzumab-dttb; Samsung Bioepsis Co)
- December 2018, Herzuma (trastuzumab-pkrb; Teva)
- December 2017, Ogivri (trastuzumab-dkst; Mylan)

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70. Ontruzant (trastuzumab-dttb). Prescribing Information. Whitehouse Station, NJ. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Revised June 2021.

71. Trazimera (trastuzumab-qyyp). Prescribing Information. New York, NY. Pfizer Labs a Division of Pfizer Inc. Revised November 2020.

72. Ogivri (trastuzumab-dkst). Prescribing Information. Morgantown, WV. Mylan Pharmaceuticals Inc. Revised November 2024.

73. Kanjinti (trastuzumab-anns). Prescribing Information. Thousand Oaks, CA. Amgen Inc. Revised December 2024.

74. Tukysa (tucatinib). Prescribing information. Bothell, WA. Seagen Inc. Revised January 2023.

75. Enhertu (fam-trastuzumab deruxtecan-nxki). Prescribing Information. Basking Ridge, NJ. Daiichi Sankyo, Inc. Revised January 2025.

76. Hercessi (trastuzumab-strf). Prescribing Information. Raleigh, NC. Accord BioPharma Inc. Revised September 2024.

History

Date	Comments
09/07/99	Add to Prescription Drug Section - New medical policy.
01/14/03	Replace Policy - Policy updated with new references; policy statement unchanged
03/08/05	Replace Policy - Policy reviewed; references added; current clinical trials and NCCN guidelines information added; policy statement unchanged.
08/09/05	Policy replaces BC.5.01.12 - New PR Policy. Policy statement changed to consider off-label uses of Trastuzumab medically necessary in tx of all stages of breast cancer with

Date	Comments
	over-expressed HER-2/neu protein, or that are FISH positive. Trastuzumab to continue to be investigational for other malignancies.
02/06/06	Codes updated - No other changes.
06/16/06	Update Scope and Disclaimer - No other changes.
08/08/06	Replace Policy - Policy reviewed with literature search; no change to policy statement.
10/09/07	Replace Policy - Policy reviewed with literature search. New FDA labeled indication noted in the Description. References added. No change to policy statement.
10/14/08	Replace Policy - Policy reviewed with literature search. Policy no longer addresses only off-label uses. Renamed "HER2 Inhibitors". Tykerb added as medically necessary when criteria are met. References and code added. Policy guidelines now state that HER2 overexpression testing is required.
12/08/09	Replace Policy - Policy reviewed with literature search. New indication: Herceptin is now considered medically necessary for gastric cancer.
05/11/10	Replace Policy - Herceptin, previously considered investigation for esophageal cancer, is now considered medically necessary.
05/10/11	Replace Policy - Policy rewritten and revised. Title changed from "HER-2 Inhibitors" to "Trastuzumab and Other HER2 Inhibitors." Components of BC.5.01.12 Trastuzumab incorporated in large part into the policy with the following variations: Lapatinib indications added. ICD-10 codes added to policy.
12/19/11	Related Policies section updated; policy 2.04.76 added.
06/26/12	Replace policy. Policy reviewed with literature search; no change in policy statements.
09/21/12	Coding Section updated – ICD-10 codes are now effective 10/01/2014.
11/13/12	Replace policy. Policy updated with new data on expanded indications of trastuzumab, coverage is expanded for adjuvant treatment of HER2 positive as either part of several different combination therapy regimens or as a single agent following prior chemotherapy; addition of criteria for pertuzumab; and treatment of HER2 positive *metastatic* breast cancer in either combination therapy or as a single agent. A medically necessary policy statement has been added for pertuzumab in the treatment of previously untreated HER2-positive breast cancer or recurrent breast cancer after adjuvant therapy, when used in combination with trastuzumab and docetaxel; all other uses are now indicated as investigational.
01/04/13	Minor update. For clarification and improved readability, the medically necessary policy statement for Pertuzumab now appears within the section addressing HER-2 positive breast cancer. No changes have been made to the policy.
07/08/13	Replace Policy. Added Policy statements and Policy Guidelines information for ado-trastuzumab emtansine. Added clinical trial info for ado-trastuzumab emtansine to the Rationale section. Updated with current NCCN for all 3 drugs.

Date	Comments
03/27/14	Coding update; HCPCS code J9306, effective 1/1/14, added to the policy.
11/10/14	Annual Review. Updated to include two medically necessary statements from current NCCN Compendium recommendations for use of trastuzumab outside of breast cancer. Codes removed with the exception of HCPCS J0306 and J9355; others are not utilized in adjudication of the policy.
02/10/15	Minor update. Clarification added to the medically necessary policy statement for pertuzumab: This includes use as adjuvant therapy, neoadjuvant therapy, and treatment of metastatic disease.
09/08/15	Annual Review. Policy updated with literature review. No change in policy statements.
01/28/16	Minor update. Added HCPCS code J9354, effective 1/1/16, to the coding table.
10/01/16	Annual Review, approved September 13, 2016. Clarification on the criteria for pertuzumab (addition of paclitaxel).
06/01/17	Annual Review, approved May 23, 2017. A statement outlining the length of therapy for initial approval has been added to the policy.
10/01/17	Interim Review, approved September 21, 2017. Added criteria for Nerlynx.
02/01/18	Interim Review, approved January 9, 2018. Revised Nerlynx (neratinib) criteria to reflect NCCN guidelines.
04/01/18	Interim Review, approved March 13, 2018. Updated Perjeta criteria to include expanded FDA label indication.
06/01/18	Annual Review, approved May 3, 2018. Updated references and per labeled indications and literature search, April 2018.
04/01/19	Interim Review, approved March 12, 2019. Added criteria for Herceptin Hylecta (trastuzumab and hyaluronidase-oysk). Added criteria for Herzuma (trastuzumab-pkrb) and Ontruzant (trastuzumab-dttb) which are both biosimilars of Herceptin (trastuzumab). Added references 67-69. Added HCPCS code J3590.
05/01/19	Annual Review, approved April 9, 2019. Added criteria for Trazimera (trastuzumab-qyyp) which is a biosimilar to Herceptin (trastuzumab). Updated criteria for Tykerb (lapatinib).
07/01/19	Coding update, added new HCPCS codes J9356, Q5112, Q5113, Q5114, and Q5115 (new codes effective 7/1/19).
08/01/19	Interim Review, approved July 9, 2019. Added criteria for Kanjinti (trastuzumab-anns) and Ogivri (trastuzumab-dkst) which are biosimilars to Herceptin (trastuzumab). Updated criteria for Kadcyla (ado-trastuzumab emtansine). Updated criteria for Herceptin (trastuzumab) and the trastuzumab biosimilars when used for conditions other than HER2-positive breast cancer. Removed HCPCS code Q5115.
10/01/19	Coding update, added HCPCS codes Q5116 and Q5117 (new codes effective 10/1/19).

Date	Comments
01/01/20	Interim Review, approved December 17, 2019, effective April 3, 2020. Added Trazimera as first-line with Herceptin.
02/01/20	Interim Review, approved, January 23, 2020. Added Enhertu (fam-trastuzumab deruxtecan -nxki) criteria.
07/01/20	Interim Review, approved June 9, 2020. Added criteria for Nerlynx (neratinib) for use in advanced or metastatic breast cancer. Added criteria for Tukysa (tucatinib) for the treatment of HER2-positive breast cancer. Removed code J3590. Added code J9358.
08/01/20	Interim Review, approved July 14, 2020. Updated Perjeta to allow coverage with trastuzumab biosimilars and removed for early breast cancer treatment reference to cancer diameter and high risk of recurrence. For Nerlynx (neratinib) added a dose limit of 240 mg (six tablets) per day. Added coverage criteria for Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) for the treatment of breast cancer. Add J3590 for Phesgo.
01/01/21	Annual Review, approved December 17, 2020. No changes to policy statements. Removed HCPCS code J3590 and added HCPCS code J9316.
03/01/21	Interim Review, approved Feb. 9, 2021. Added generic lapatinib to policy with same covered indications as Tykerb (lapatinib). Updated Tykerb (lapatinib) coverage criteria removing two non-FDA approved indications for adjuvant treatment of HER2-positive breast cancer (node positive or negative) as part of several different combination therapy regimens following prior chemotherapy and for treatment of HER2-positive metastatic breast cancer in combination therapy. Added requirement to Tykerb to require generic lapatinib first and placed a dose limit of 1,500 mg per day. Added a new indication to Enhertu (fam-trastuzumab deruxtecan-nxki) for the treatment of gastric or GEJ adenocarcinoma. Added coverage criteria for Margenza (margetuximab-cmkb) for the treatment of metastatic HER2-positive breast cancer. Added HCPCS code J3590.
04/01/21	Update Related Policies. Policy 2.04.76 archived and references removed.
01/01/22	Annual Review, approved December 2, 2021. No changes to policy statements.
07/01/22	Annual Review, approved June 14, 2022. Moved Ogivri (trastuzumab-dkst) to being a preferred trastuzumab product. Updated coverage criteria for the non-preferred products Herzuma, Kanjinti, and Ontruzant to require the patient has had an adequate trial and failure with Herceptin, Ogivri, or Trazimera. Updated Enhertu (fam-trastuzumab deruxtecan-nxki) indication for the treatment of metastatic breast cancer and added coverage for use in the neoadjuvant or adjuvant setting. Added to Herzuma (trastuzumab-pkrb) coverage for the treatment of metastatic gastric cancer. Added a note to Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) that switching therapy from Perjeta and/or a trastuzumab product to Phesgo during treatment is allowed. Added HCPCS code J9353 and removed HCPCS code J3590.

Date	Comments
10/01/22	Interim Review, approved September 13, 2022. Added coverage for Enhertu (fam-trastuzumab deruxtecan-nxki) for adults with unresectable or metastatic HER2-low breast cancer and unresectable or metastatic non-small cell lung cancer.
06/01/23	Annual Review, approved May 9, 2023. Added coverage criteria for Tukysa when used in combination with trastuzumab, for adult individuals with RAS wild-type, HER2-positive unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy. Changed "patient" to "individual" throughout the policy for the standardization.
09/01/23	Interim Review, approved August 8, 2023. Moved Trazimera to second-line (non-preferred) agent, effective January 1, 2024, following a 90-day provider notification due to changes in the preferred medical benefit drugs.
04/01/24	Annual Review, approved March 25, 2024. Minor correction made to add the quantity limit requirement for Tukysa (tucatinib) to the colorectal cancer coverage criteria.
08/01/24	Interim Review, approved July 9, 2024. Updated Enhertu (fam-trastuzumab deruxtecan-nxki) coverage criteria to include treatment of certain individuals with a unresectable or metastatic solid tumor. Added Hercessi (trastuzumab-strf) as a second line trastuzumab product. Added HCPCS code J3590 to report Hercessi.
10/01/24	Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Changed Kanjinti (trastuzumab-anns) and Trazimera (trastuzumab-qyyp) to preferred trastuzumab products. Changed Herceptin (trastuzumab), Herceptin Hylecta (trastuzumab and hyaluronidase-oysk), and Ogivri (trastuzumab-dkst) to non-preferred trastuzumab products. Updated coverage criteria for Herceptin, Herceptin Hylecta, Hercessi (trastuzumab-strf), Herzuma (trastuzumab-pkrb), Ogivri, and Ontruzant (trastuzumab-dttb) to require the individual to have had an adequate trial and failure with Kanjinti or Trazimera.
01/01/25	Coding update. Added new HCPCS code Q5146 effective 1/1/2025.
04/01/25	Annual Review, approved March 11, 2025. Added a new indication to Enhertu (fam-trastuzumab deruxtecan-nxki) for the treatment of adult individuals with HR-positive HER2-low or HER2-ultralow breast cancer that has progressed on one or more endocrine therapies in the metastatic setting. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated policy title from Herceptin (trastuzumab) and Other HER2 Inhibitors to HER2 Inhibitors.

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