CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Trastuzumab and Biosimilars

Trastuzumab (Herceptin®)

Trastuzumab-anns (Kanjinti®)

Trastuzumab-dkst (Ogivri®)

Trastuzumab-dttb (Ontruzant®)

Trastuzumab-pkrb (Herzuma®)

Trastuzumab-qyyp (Trazimera®)

Trastuzumab-strf (Hercessi®)

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Trastuzumab (Herceptin®), Trastuzumab-anns (Kanjinti®), Trastuzumab-dkst (Ogivri®), Trastuzumab-dttb (Ontruzant®), Trastuzumab-pkrb (Herzuma®), Trastuzumab-qyyp (Trazimera®), Trastuzumab-strf (Hercessi®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Trastuzumab (Herceptin), Trastuzumab-anns (Kanjinti), Trastuzumab-dkst (Ogivri), Trastuzumab-dttb (Ontruzant), Trastuzumab-pkrb (Herzuma), Trastuzumab-qyyp (Trazimera), Trastuzumab-strf (Hercessi®): Discussion

Trastuzumab is a monoclonal antibody specifically designed to target HER2 receptors, which are transmembrane protein receptors on both normal cells and HER2+ tumor cells. HER2 plays an important role in the signaling network that drives cell growth. Trastuzumab blocks intracellular signaling pathways which may promote cell death and arrest cell growth.
Trastuzumab also flags the tumor cell for destruction by the body's immune system, known as antibody-dependent cellular cytotoxicity (ADCC). Activation of natural killer cells is what leads to ADCC. In addition, trastuzumab prevents HER2 shedding (amount of HER2 concentration in the blood). The potential clinical value is based on observations that high serum levels of HER2 extracellular area correlate with poor prognosis and decreased responsiveness to endocrine therapy and chemotherapy in those with advanced cancer.[1]

Trastuzumab biosimilars are biological medicinal products with structural and functional properties, including pharmacokinetics and clinical efficacy, like that of an approved biological reference medical product, trastuzumab.[2]

Therapy with trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab products can also cause an asymptomatic decline in left ventricular ejection fraction (LVEF). The greatest risk is when administered concurrently with an anthracycline. Infusion reactions with trastuzumab products can consist of a symptom complex characterized by fever and chills, and on occasion include nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. Pulmonary toxicity can be serious and fatal. It can include dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress

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syndrome, and pulmonary fibrosis. Such events can occur because of infusion reactions. Other side effects include embryo-fetal toxicity and hypersensitivity reactions.[3,4,5,6,7,8,20]

The National Comprehensive Cancer Network (NCCN) endorses trastuzumab in the following cancer types: biliary tract cancers, breast cancer, central nervous system cancers, colon cancer, esophageal and esophagogastric junction cancers, gastric cancer, head and neck cancers, rectal cancer, and uterine neoplasms. [9,10,11,12,13,14,15,16,17]

Trastuzumab and biosimilars: Definitions

- **Antibody-dependent cellular cytotoxicity (ADCC)** - A type of immune reaction in which a target cell or microbe is coated with antibodies and killed by certain types of white blood cells. The white blood cells bind to the antibodies and release substances that kill the target cells or microbes.[18]
- **Biosimilar drug** - A biological drug that is very much like another biological drug (called the reference drug) that has already been approved by the U.S. Food and Drug Administration (FDA). To be called a biosimilar drug, a biological drug must be shown to be as safe as, work as well as, and work in the same way as its reference drug. It must also be used in the same way, at the same dose, and for the same condition as the reference drug. Biosimilar drugs must be approved by the FDA and may cost less than the reference drugs.[19]
- **BRAF gene** - A gene that encodes a protein belonging to the RAF family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion.
- **Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)** - When the microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of the mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Human Epidermal Growth Factor Receptor 2 (HER2)** - A protein involved in normal cell growth. HER2/neu may be made in larger than normal amounts by some types of cancer cells, including breast, ovarian, bladder, pancreatic, stomach, and esophageal cancers. This may cause cancer cells to grow more quickly and spread to other parts of the body.
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than thirty leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

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- **Proficient mismatch repair/microsatellite-stable (pMMR/MMS)** - When microsatellite DNA segments are unchanged (not mutated), the tumor cells are considered microsatellite stable (MSS) or have proficient mismatch repair. MSS cancers have normal levels of mismatch repair gene and protein expression and can correct DNA mismatch repair errors proficiently.
- **RAS gene** - A family of genes that make proteins involved in cell signaling pathways that control cell growth and cell death. Mutated (changed) forms of the RAS gene may be found in some types of cancer. These changes may cause cancer cells to grow and spread in the body. Members of the RAS gene family include KRAS, HRAS, and NRAS.
- **Wild-type** - The natural, unchanged (unmutated) form of the gene.

Trastuzumab and biosimilars: Policy

Note: Coverage of trastuzumab will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Trastuzumab and biosimilars will be considered for coverage when the following criteria are met:

Biliary Tract Cancers

(Extrahepatic and Intrahepatic Cholangiocarcinoma, Gallbladder Cancer)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent treatment in combination with pertuzumab for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease that is HER2-positive [9]

Breast Cancer – Invasive (Neoadjuvant and Adjuvant)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** Required criteria coverage:

3. Single agent for treatment of HER2-overexpressing breast cancer[3,4,5,6,7,8,20]; OR

For **NCCN** required criteria coverage:

4. Preoperative systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and locally advanced c≥T2 or cN+ and M0 disease, or cT1c, cN0 disease as a component of one of the following:
   a) TCH (docetaxel, carboplatin, and trastuzumab) regimen
   b) TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) regimen; OR

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5. Preoperative systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and locally advanced c≥T2 or cN+ and M0 disease, or cT1c, cN0 disease in combination with one of the following:
   a) Paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks)
   b) Paclitaxel and pertuzumab following AC regimen (dose-dense or every 3 weeks)
   c) Docetaxel with or without pertuzumab following AC regimen
   d) Docetaxel and cyclophosphamide
   e) Paclitaxel and pertuzumab; OR
6. Adjuvant systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and cT1c-3, cN0 or N+, M0 (pT1-3 and pN0 or pN+ tumors) disease in combination with one of the following:
   a) Paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks)
   b) Docetaxel following AC regimen
   c) Docetaxel and cyclophosphamide
   d) Pertuzumab and paclitaxel following AC regimen (dose-dense or every 3 weeks) for node-positive tumors only
   e) Pertuzumab and docetaxel following AC regimen for node-positive tumors only
   f) Paclitaxel and pertuzumab for node-positive tumors only
   g) Paclitaxel for low-risk T1, N0, M0, HER2-positive tumors for patients not eligible for other standard adjuvant regimens due to comorbidities; OR
7. Adjuvant systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and cT1c-3, cN0 or N+, M0 (pT1-3 and pN0 or pN+ tumors) disease as a component of one of the following:
   a) TCH (docetaxel, carboplatin, and trastuzumab) regimen;
   b) TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) regimen for node-positive tumors only; OR

   Note:

   1. It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC
   2. If there is no residual disease after preoperative therapy or no preoperative therapy, complete up to one year of HER2 targeted therapy with trastuzumab with or without pertuzumab after completing the planned chemotherapy regimen course. If residual disease is present after preoperative therapy and ado-trastuzumab emtansine is discontinued for toxicity, then trastuzumab with or without pertuzumab to complete one year of therapy can be used.

8. Adjuvant systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and locally advanced c≥T2 or cN+ and M0 disease, or cT1c, cN0 disease following completion of planned chemotherapy and following mastectomy or breast-conserving surgery (BCS) with surgical axillary staging with or without one of the following:
   a) Pertuzumab if hormone receptor negative and ypT0N0 or pCR

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b) Pertuzumab if hormone receptor negative and ypT1-4N0 or ypN≥1 (if ado-trastuzumab discontinued for toxicity)
c) Pertuzumab if hormone receptor-positive and ypT0N0 or pCR; OR

9. Adjuvant systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and locally advanced c≥T2 or cN+ and M0 disease, or cT1c, cN0 disease following completion of planned chemotherapy and following mastectomy or breast-conserving surgery (BCS) with surgical axillary staging with one of the following:
   a) Pertuzumab if hormone receptor-positive and ypT0N0 or pCR and node-positive at initial staging
   b) Pertuzumab if hormone receptor negative and ypT1-4N0 or ypN≥1 and node-positive at initial staging (if ado-trastuzumab discontinued for toxicity).

Inflammatory Breast Cancer (Neoadjuvant and Adjuvant)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Preoperative systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive disease in combination with one of the following:
   a) Paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks)
   b) Paclitaxel and pertuzumab following AC regimen (dose-dense or every 3 weeks)
   c) Docetaxel with or without pertuzumab following AC regimen
   d) Docetaxel and cyclophosphamide
   e) Paclitaxel and pertuzumab; OR
4. Preoperative systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive disease as a component of one of the following:
   a) TCH (docetaxel, carboplatin, and trastuzumab) regimen
   b) TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) regimen; OR
5. Adjuvant systemic therapy for patients who had a response to preoperative systemic therapy, followed by surgery, and need to complete planned chemotherapy, for human epidermal growth factor receptor 2 (HER2)-positive tumors in combination with one of the following:
   a) Paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks)
   b) Docetaxel following AC regimen
   c) Docetaxel and cyclophosphamide
   d) Pertuzumab and paclitaxel following AC regimen (dose-dense or every 3 weeks) for node-positive tumors only
   e) Pertuzumab and docetaxel following AC regimen for node-positive tumors only
   f) Paclitaxel and pertuzumab for node-positive tumors only
   g) Paclitaxel for low-risk T1, N0, M0, HER2-positive tumors for patients not eligible for other standard adjuvant regimens due to comorbidities; OR
6. Adjuvant systemic therapy for patients who had a response to preoperative systemic therapy, followed by surgery, and need to complete planned chemotherapy, for human

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epidermal growth factor receptor 2 (HER2)-positive tumors as a component of one of the following:
a) TCH (docetaxel, carboplatin, and trastuzumab) regimen
b) TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) regimen for node-positive tumors only

Note:

1. It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.
2. If there is no residual disease after preoperative therapy or no preoperative therapy, complete up to one year of HER2 targeted therapy with trastuzumab with or without pertuzumab after completing the planned chemotherapy regimen course. If residual disease is present after preoperative therapy and ado-trastuzumab emtansine is discontinued for toxicity, then trastuzumab with or without pertuzumab to complete one year of therapy can be used.

Breast Cancer – Invasive and Inflammatory

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Used for patients with no response to preoperative systemic therapy (inflammatory only), or recurrent unresectable (local or regional) or stage IV (M1) human epidermal growth factor receptor 2 (HER2)- positive disease that is either hormone receptor-negative or hormone receptor-positive with or without endocrine therapy as one of the following:
   a) First-line therapy in combination with pertuzumab with either docetaxel or paclitaxel
   b) Fourth-line therapy and beyond in combination with docetaxel, vinorelbine, or capecitabine, or with paclitaxel with or without carboplatin
   c) Fourth-line therapy and beyond in combination with cyclophosphamide, eribulin, gemcitabine, ixabepilone, lapatinib (without cytotoxic therapy), or albumin-bound paclitaxel
   d) In combination with pertuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab; OR
4. Third-line therapy and beyond (may also be given in the second-line setting) in combination with capecitabine and tucatinib (in patients with both systemic and CNS progression in the third-line setting and beyond) for inflammatory disease with no response to preoperative systemic therapy, or recurrent unresectable (local or regional) or stage IV (M1) human epidermal growth factor receptor 2 (HER2)-positive disease that is one of the following:
   a) Hormone receptor-negative
   b) Hormone receptor-positive with or without endocrine therapy; OR

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5. Used in combination with tamoxifen, fulvestrant, or aromatase inhibition with or without lapatinib, for the treatment of recurrent unresectable (local or regional) or stage IV (M1) hormone receptor-positive human epidermal growth factor receptor 2 (HER2)-positive disease in postmenopausal women or premenopausal women treated with ovarian ablation/suppression; OR
6. Treatment for recurrent unresectable (local or regional) or stage IV (M1) hormone receptor-positive human epidermal growth factor receptor 2 (HER2)-positive disease in combination with tamoxifen for premenopausal women without ovarian ablation/suppression; OR
7. Emerging biomarkers to identify novel therapies for stage IV (M1) disease: Activity in HER2 activating mutations in combination with neratinib and fulvestrant for one of the following:
   a) Hormone receptor-positive human epidermal growth factor receptor 2 (HER2)-negative disease who have already received a CDK4/6 inhibitor therapy
   b) Triple-negative disease.[10]

Note: Men with breast cancer should be treated similarly to postmenopausal women. The use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis.

Central Nervous System Cancers

Extensive Brain Metastases

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Used in combination with capecitabine and tucatinib as the treatment for extensive brain metastases in HER2-positive breast cancer if previously treated with one or more anti-HER2-based regimens in one of the following:
   a) As primary treatment in select cases (e.g., small asymptomatic brain metastases)
   b) As treatment for recurrent disease with stable systemic disease or reasonable systemic treatment options; OR
4. Used in high doses in combination with pertuzumab as the treatment for extensive brain metastases in HER2-positive breast cancer in one of the following:
   a) As primary treatment in select cases (e.g., small asymptomatic brain metastases)
   b) As treatment for recurrent disease with stable systemic disease or reasonable systemic treatment options.

Limited Brain Metastases

1. At least 18 years of age; AND

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2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Used in combination with capecitabine and tucatinib as a treatment for limited brain metastases in HER2-positive breast cancer if previously treated with one or more anti-HER2-based regimens in one of the following:
   a) As initial treatment in select cases (e.g., small asymptomatic brain metastases)
   b) As treatment for recurrent brain metastases
   c) Treatment of relapsed disease with either stable systemic disease or reasonable systemic treatment options; OR
4. Used in high doses in combination with pertuzumab as a treatment for limited brain metastases in HER2-positive breast cancer in one of the following:
   a) As primary treatment in select cases (e.g., small asymptomatic brain metastases)
   b) As treatment for recurrent brain metastases
   c) Treatment of relapsed disease with either stable systemic disease or reasonable systemic treatment options.

Leptomeningeal Metastases

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Intra-cerebrospinal fluid (CSF) treatment for leptomeningeal metastases from HER2-positive breast cancer in any one of the following:
   a) Primary treatment in patients with good risk status (KPS ≥60), no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment
   b) Maintenance treatment in patients with negative CSF cytology or in clinically stable patients with persistently positive CSF cytology.[11]

Colon Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. If intensive therapy is not recommended, may be given in combination with pertuzumab, lapatinib, or tucatinib (HER2-amplified and RAS and BRAF wild-type) in one of the following:
   a) As adjuvant treatment following resection and/or local therapy for resectable metachronous metastases who have received previous chemotherapy (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or POLE/POLD1 mutation)

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b) As adjuvant treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy (dMMR/MSI-H or POLE/POLD1 mutation)
c) As adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after initial treatment. Biologic therapy is only appropriate for continuation of favorable response from conversion therapy. (pMMR/MSS or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H or POLE/POLD1 mutation); OR

4. If intensive therapy is not recommended and there is no previous treatment with a HER2 inhibitor, may give in combination with pertuzumab, lapatinib, or tucatinib (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on a checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) for one of the following:
   a) Primary treatment for locally unresectable or medically inoperable disease
   b) Primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for existing or imminent obstruction
   c) Synchronous unresectable metastases of other sites
   d) Initial treatment for unresectable metachronous metastases in patients who have not received previous FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy; OR
5. Initial treatment in combination with pertuzumab, lapatinib, or tucatinib (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) for patients with unresectable metachronous metastases and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
6. Subsequent therapy in combination with pertuzumab, lapatinib, or tucatinib for progression of advanced or metastatic disease (HER2-amplified and RAS and BRAF wild type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) not previously treated with HER2 inhibitor, in patients previously treated with one of the following:
   a) Oxaliplatin-based therapy without irinotecan
   b) Irinotecan-based therapy without oxaliplatin
   c) Oxaliplatin and irinotecan; OR
7. Subsequent therapy in combination with pertuzumab, lapatinib, or tucatinib for progression of advanced or metastatic disease (HER2-amplified and RAS and BRAF wild type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) not previously treated with HER2 inhibitor, in patients previously treated without one of the following:

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a) Irinotecan or oxaliplatin
b) Irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab

Colon Cancer - Appendiceal Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Initial systemic therapy for advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) (HER2-amplified and RAS and BRAF wild-type) in combination with pertuzumab, lapatinib, or tucatinib if intensive therapy not recommended and no previous treatment with a HER2 inhibitor; OR
4. Subsequent therapy (biomarker-directed) in combination with pertuzumab, lapatinib, or tucatinib for progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) or polymerase epsilon/delta [POLE/POLD1] mutation (HER2-amplified and RAS and BRAF wild type) not previously treated with HER2 inhibitor, in patients previously treated with one of the following:
   a) Oxaliplatin-based therapy without irinotecan
   b) Irinotecan-based therapy without oxaliplatin
   c) Oxaliplatin and irinotecan; OR
5. Subsequent therapy in combination with pertuzumab, lapatinib, or tucatinib for progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) (HER2-amplified and RAS and BRAF wild type) not previously treated with HER2 inhibitor, in patients previously treated without one of the following:
   a) Irinotecan or oxaliplatin
   b) Irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab.[12]

Esophageal and Esophagogastric Junction Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Induction systemic therapy for relieving dysphagia in select patients with HER2 overexpression positive adenocarcinoma who are medically fit and planned for

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esophagectomy with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, any N disease in combination with one of the following:
   a) Fluorouracil or capecitabine and oxaliplatin or cisplatin and pembrolizumab (PD-L1 CPS ≥1)
   b) Fluorouracil or capecitabine and oxaliplatin or cisplatin
   c) Fluorouracil and irinotecan
   d) Paclitaxel with or without carboplatin or cisplatin
   e) Docetaxel with or without cisplatin
   f) Fluorouracil
   g) Capecitabine
   h) Docetaxel, cisplatin or oxaliplatin, and fluorouracil
4. Palliative therapy for patients who are not surgical candidates or have an unresectable locally advanced, recurrent, or metastatic disease with HER2 overexpression positive adenocarcinoma and Karnofsky performance score ≥60% or ECOG performance score ≤2 as first-line therapy in combination with systemic chemotherapy with one of the following:
   a) Fluorouracil or capecitabine and oxaliplatin or cisplatin
   b) Fluorouracil and irinotecan
   c) Paclitaxel with or without carboplatin or cisplatin
   d) Docetaxel with or without cisplatin
   e) Fluorouracil
   f) Capecitabine
   g) Docetaxel, cisplatin or oxaliplatin, and fluorouracil; OR
5. Palliative therapy for HER2 overexpression-positive adenocarcinoma patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and Karnofsky performance score ≥60% or ECOG performance score ≤2 as first-line therapy in combination with one of the following:
   a) Fluorouracil, cisplatin or oxaliplatin, and pembrolizumab (if no prior tumor progression while on therapy with a checkpoint inhibitor)
   b) Capecitabine, cisplatin or oxaliplatin, and pembrolizumab (if no prior tumor progression while on therapy with a checkpoint inhibitor).[13]

Gastric Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma[3,4,5,6,7,8,20]; OR

For **NCCN** required criteria coverage:

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4. Primary treatment in combination with systemic chemotherapy for patients who are medically fit for surgery but with surgically unresectable locoregional HER2 overexpression-positive adenocarcinoma with one of the following:
   a) Fluorouracil or capecitabine and oxaliplatin or cisplatin
   b) Fluorouracil and irinotecan
   c) Paclitaxel with or without carboplatin or cisplatin
   d) Docetaxel with or without cisplatin
   e) Fluorouracil
   f) Capecitabine
   g) Docetaxel, cisplatin or oxaliplatin, and fluorouracil; OR
5. Primary treatment for patients who are medically fit for surgery but with surgically unresectable locoregional HER2 overexpression-positive adenocarcinoma in combination with one of the following:
   a) Cisplatin, pembrolizumab and fluorouracil or capecitabine
   b) Oxaliplatin, pembrolizumab and fluorouracil or capecitabine; OR
6. Early-stage gastric HER2 overexpression positive adenocarcinoma and PD-L1 CPS ≥ 1 with endoscopic features suggestive of deep submucosal invasion including converging folds, irregular surface pattern, and ulceration in a large gastric mass with favorable histology and completed an endoscopic resection, consider systemic therapy in combination with one of the following:
   a) cisplatin, pembrolizumab and fluorouracil or capecitabine
   b) oxaliplatin, pembrolizumab and fluorouracil or capecitabine; OR
7. Palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease with HER2 overexpression positive adenocarcinoma and Karnofsky performance score ≥60% or ECOG performance score ≤2 as first-line therapy in combination with systemic chemotherapy in one of the following:
   a) Cisplatin and fluorouracil or capecitabine
   b) Oxaliplatin and fluorouracil or capecitabine
   c) fluorouracil and irinotecan
   d) paclitaxel with or without carboplatin or cisplatin
   e) docetaxel with or without cisplatin
   f) fluorouracil
   g) capecitabine
   h) docetaxel, cisplatin or oxaliplatin, and fluorouracil
   i) Cisplatin, pembrolizumab, and fluorouracil or capecitabine (if no prior tumor progression while on therapy with a checkpoint inhibitor)
   j) Oxaliplatin, pembrolizumab, and fluorouracil or capecitabine (if no prior tumor progression while on therapy with a checkpoint inhibitor).[14]

Head and Neck Cancers - Salivary Gland Tumors

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

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For **NCCN** required criteria coverage:

3. Systemic therapy as a single agent, in combination with docetaxel, or in combination with pertuzumab for human epidermal growth factor receptor 2 (HER2)-positive recurrent disease with one of the following:
   a) Distant metastases in patients with a performance status (PS) of 0-3
   b) Unresectable locoregional recurrence or second primary with prior radiation therapy.[15]

Rectal Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. If intensive therapy is not recommended may be given in combination with pertuzumab, lapatinib, or tucatinib (HER2-amplified and RAS and BRAF wild-type) for one of the following as adjuvant treatment:
   a) Following resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or POLE/POLD1 mutation)
   b) Following resection and/or local therapy) for resectable metachronous metastases in patients who have received previous immunotherapy (dMMR/MSI-H or POLE/POLD1 mutation)
   c) For unresectable metachronous metastases that converted to resectable disease after initial treatment. Biologic therapy is only appropriate for the continuation of a favorable response from conversion therapy. (pMMR/MSS only or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H or POLE/POLD1 mutation); OR
4. Therapy in combination with pertuzumab, lapatinib or tucatinib (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) if intensive therapy not recommended and no previous treatment with a HER2 inhibitor for one of the following:
   a) Primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for existing or imminent obstruction
   b) Primary treatment for synchronous unresectable metastases of other sites
   c) Primary treatment for unresectable isolated pelvic/anastomotic recurrence
   d) Initial treatment for unresectable metachronous metastases in patients who have not received previous FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy; OR

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5. Primary treatment in combination with pertuzumab, lapatinib, or tucatinib for T3, Any N; T1-2, N1-2; T4, Any N; or locally unresectable or medically inoperable disease (HER2-amplified and RAS and BRAF wild type only) if resection is contraindicated following total neoadjuvant therapy (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) or neoadjuvant/definitive immunotherapy (dMMR/MSI-H only) if intensive therapy not recommended; OR
6. Initial treatment in combination with pertuzumab, lapatinib, or tucatinib (HER2-amplified and RAS and BRAF wild-type) with unresectable metachronous metastases (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
7. Subsequent therapy in combination with pertuzumab, lapatinib, or tucatinib for progression of advanced or metastatic disease (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) not previously treated with HER2 inhibitor, in patients previously treated with one of the following:
   a) Oxaliplatin-based therapy without irinotecan
   b) Irinotecan-based therapy without oxaliplatin
   c) Oxaliplatin and irinotecan; OR
8. Subsequent therapy in combination with pertuzumab, lapatinib, or tucatinib for progression of advanced or metastatic disease (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) not previously treated with HER2 inhibitor, in patients previously treated without one of the following:
   a) Irinotecan or oxaliplatin
   b) Irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab.[16]

Uterine Neoplasms - Endometrial Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Used in combination with carboplatin and paclitaxel and continued as a single agent for maintenance therapy for stage III/IV HER2-positive uterine serous carcinoma or carcinosarcoma in one of the following:

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a) That is suitable for primary surgery as additional treatment with or without sequential external beam radiation therapy (EBRT) and with or without vaginal brachytherapy after total hysterectomy/bilateral salpingo-oophorectomy (TH/BSO)
b) That is not suitable for primary surgery as primary treatment with or without sequential EBRT and with or without brachytherapy; OR

4. First-line therapy if no prior trastuzumab therapy (or second-line or subsequent therapy if no prior trastuzumab therapy) in combination with carboplatin and paclitaxel for recurrent HER2-positive uterine serous carcinoma or carcinosarcoma in one of the following:
   a) Isolated metastases
   b) For disseminated metastases with or without sequential palliative external beam radiation therapy (EBRT)
   c) With sequential EBRT and with or without brachytherapy for locoregional recurrence with no prior RT to the site of recurrence, or previous brachytherapy only
   d) With sequential EBRT for locoregional recurrence with disease confined to the vagina or paravaginal soft tissue, or in pelvic, para-aortic, or common iliac lymph nodes, after surgical resection
   e) With or without sequential EBRT for locoregional recurrence with upper abdominal or peritoneal disease after surgical resection
   f) With or without sequential palliative EBRT or brachytherapy for locoregional recurrence in patients who have received prior EBRT to the site of recurrence.[17]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Trastuzumab and biosimilars: References

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Trastuzumab and biosimilars: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	DESCRIPTION
C08.9	Salivary Gland Tumors
C15.5	Esophageal Cancer
C16.9	Gastric Cancer
C18.1	Appendiceal Cancer
C18.9	Colon Cancer
C20.0	Rectal Cancer
C24.9	Biliary Tract Cancer
C50.9	Malignant neoplasm of breast of unspecified site
C54.1	Endometrial Carcinoma
C72.9	Malignant neoplasm of central nervous system, unspecified
C79.31	Brain Metastases - Limited
C79.32	Leptomeningeal Metastases
C76.0	Head and Neck Cancer
J9355	Trastuzumab (Herceptin)
Q5117	Trastuzumab-anns (Kanjinti)
Q5114	Trastuzumab-dkst (Ogivri)
Q5112	Trastuzumab-dttb (Ontruzant)
Q5113	Trastuzumab-pkrb (Herzuma)
Q5116	Trastuzumab-qyyp (Trazimera)

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Q5146	Trastuzumab-strf (Hercessi)

Trastuzumab and biosimilars: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	7/20/2023, 10/17/2024
3	Policy Revision Dates:	10/17/2024
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	10/23/2023, 10/29/2024
6	Revision Changes:	10/17/2024 - Added a new biosimilar - trastuzumab-strf (Hercessi), adverse reactions, and one indication for gastric cancer

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