Trastuzumab:
Herceptin®; Ogivri®; Kanjinti®; Trazimera™; Herzuma®; Ontruzant®; Hercessi™
(Intravenous)

-E-

Document Number: EOCCO-0413

Date Approved: 01/06/2025

Date of Origin: 01/07/2019

Dates Reviewed: 01/2019, 04/2019, 07/2019, 10/2019, 11/2019, 01/2020, 04/2020, 07/2020, 10/2020, 01/2021, 05/2021, 07/2021, 10/2021, 02/2022, 03/2022, 07/2022, 10/2022, 01/2023, 04/2023, 07/2023, 10/2023, 01/2024, 04/2024, 07/2024, 10/2024, 12/2024

I. Length of Authorization [1-6,8]

Coverage is provided for 6 months and may be renewed (unless otherwise specified).

- Neoadjuvant/preoperative and adjuvant treatment in Breast Cancer may be authorized up to a maximum of fifty-two (52) weeks of treatment.

II. Dosing Limits

1. Max Units (per dose and over time) [HCPCS Unit]:

- Herceptin (150 mg SDV):
  - Gastric, Esophageal, and Esophagogastric Junction Cancer:
    - Load: 90 billable units x 1 dose
    - Maintenance: 75 billable units every 14 days
  - CNS Cancer: 300 billable units every 28 days
  - Breast Cancer, Colorectal Cancer, & Appendiceal Adenocarcinoma, All other indications: 90 billable units every 21 days
- Ogivri, Kanjinti, Trazimera, Herzuma, Ontruzant, Hercessi (420 mg MDV):
  - Gastric, Esophageal, and Esophagogastric Junction Cancer:
    - Load: 92 billable units x 1 dose
    - Maintenance: 69 billable units every 14 days
  - CNS Cancer: 276 billable units every 28 days
  - Breast Cancer, Colorectal Cancer, & Appendiceal Adenocarcinoma, All other indications: 92 billable units every 21 days

III. Initial Approval Criteria [1-7]

Coverage is provided in the following conditions:

Requests for Herceptin, Herzuma, Kanjinti, or Ontruzant:

- Patients must have failed, or have a contraindication or intolerance to Ogivri (trastuzumab-dkst) AND Trazimera (trastuzumab-qyyp); **AND**

- Patient is at least 18 years of age; **AND**

Universal Criteria [1-7]

- Left ventricular ejection fraction (LVEF) is within normal limits prior to initiating therapy and will be assessed at regular intervals (e.g., every 3 months) during treatment; **AND**
- Patient has human epidermal growth factor receptor 2 (HER2)-positive* disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Females of reproductive potential have a negative pregnancy test prior to initiating treatment and will use effective contraception during treatment and for 7 months after the last dose; **AND**
- Therapy will not be substituted with or for ado-trastuzumab emtansine (Kadcyla) or fam-trastuzumab deruxtecan-nxki (Enhertu); **AND**
- Therapy will not be used in combination with trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or pertuzumab/trastuzumab and hyaluronidase-zzxf (Phesgo); **AND**

Breast Cancer † ‡ [1-9,11-17,36-39,44-45,10e,11e,13e,14e,16e,17e,19e,20e]

- Used as adjuvant therapy; **AND**
  - Patient has ≥ T1 disease, node positive disease, or inflammatory disease; **AND**
    - Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) WITH pertuzumab *(cN+ or pN+ ONLY)*; **OR**
    - Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) WITHOUT pertuzumab; **OR**
    - Used in combination with pertuzumab *(cN+ or pN+ ONLY)*; **OR**
    - Used as a single agent; **OR**
  - Used after completion of planned chemotherapy and following mastectomy or breast-conserving surgery; **AND**
    - Patient has ≥ ypT0N0 or pCR disease by axillary staging; **AND**
    - Used as a single agent or in combination with pertuzumab; **OR**
- Used as neoadjuvant or preoperative therapy; **AND**
  - Patient has ≥ T1c disease, node positive disease, or inflammatory disease; **AND**

- Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) with or without pertuzumab; **OR**

- Used for recurrent unresectable (local or regional) or metastatic disease OR inflammatory breast cancer **Ω**; **AND**
  - Used as a single agent in patients who have received one or more prior chemotherapy regimens for metastatic disease **†**; **OR**
  - Used in combination with one of the following:
    - Paclitaxel as first-line therapy for metastatic disease **†**
    - Endocrine therapy (e.g., tamoxifen, fulvestrant, or aromatase inhibition with or without lapatinib) in patients with hormone receptor-positive disease; **AND**
      - Patient is postmenopausal; **OR**
      - Patient is premenopausal and is treated with ovarian ablation/suppression; **OR**
      - Patient is premenopausal and will not receive ovarian ablation/suppression *(with tamoxifen ONLY)*; **OR**
      - Patient is a male (sex assigned at birth) **¥**
    - Pertuzumab and a taxane (e.g., docetaxel, paclitaxel) as first-line therapy
    - Capecitabine and tucatinib as second-line therapy and beyond after prior HER2-directed therapy with trastuzumab, pertuzumab, AND ado-trastuzumab emtansine
    - Cytotoxic chemotherapy as fourth-line therapy and beyond
    - Lapatinib (without cytotoxic therapy) as fourth-line therapy and beyond after prior anti-HER2 directed therapy for metastatic disease
    - Pertuzumab with or without cytotoxic therapy as subsequent therapy in patients previously treated with chemotherapy and trastuzumab (without pertuzumab)

***¥** When an aromatase inhibitor is used in males, suppression of testicular steroidogenesis with a GnRH analog is required.*

Central Nervous System (CNS) Cancer ‡ [8,19,30-31]

- Patient has leptomeningeal metastases from breast cancer **Ω**; **AND**
  - Trastuzumab will be administered intrathecally or intraventricularly; **AND**
    - Used as primary treatment in patients with good risk status (i.e., KPS ≥60, no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options if needed); **OR**
    - Used as maintenance therapy in patient with negative CSF cytology or in clinically stable patient with persistently positive CSF cytology; **OR**
- Patient has brain metastases from breast cancer; **AND**

- Used in combination with capecitabine and tucatinib in patients previously treated with trastuzumab, pertuzumab, AND ado-trastuzumab; **AND**
- Used in one of the following treatment settings:
  - Used as initial treatment in patients with small asymptomatic brain metastases
  - Patient has recurrent limited brain metastases
  - Patient has recurrent extensive brain metastases with stable systemic disease or reasonable systemic treatment options
  - Patient has relapsed limited brain metastases with either stable systemic disease or reasonable systemic treatment options

Gastric, Esophageal, and Esophagogastric Junction Cancers † ‡ Φ [1-8,18,33,34,51,34e,35e]

- Patient has adenocarcinoma; **AND**
  - Used as induction systemic therapy for relieving dysphagia (*applies to Esophageal and Esophagogastric Junction Cancers ONLY*) **Ω**; **AND**
    - Patient is medically fit and planned for esophagectomy with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3 cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, Any N disease; **AND**
      - Used in combination with chemotherapy; **OR**
      - Used in combination with pembrolizumab, fluoropyrimidine- and platinum-containing chemotherapy; **AND**
        - Tumor expresses PD-L1 (CPS ≥ 1) as determined by an FDA-approved or CLIA compliant test❖; **OR**
  - Patient has early-stage disease* with favorable histology *(applies to Gastric Cancer ONLY)* **Ω**; **AND**
    - Patient has completed an endoscopic resection; **AND**
      - Used in combination with chemotherapy; **OR**
      - Used in combination with pembrolizumab, fluoropyrimidine- and platinum-containing chemotherapy; **AND**
        - Tumor expresses PD-L1 (CPS ≥ 1) as determined by an FDA-approved or CLIA compliant test❖; **OR**
  - Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; **AND**
    - Used as first-line therapy; **AND**
      - Used in combination with oxaliplatin or cisplatin AND fluorouracil or capecitabine; **OR**

- Used in combination with pembrolizumab AND fluorouracil or capecitabine AND oxaliplatin or cisplatin; **AND**
  - Tumor expresses PD-L1 (CPS ≥ 1) as determined by an FDA-approved or CLIA compliant test❖

** Endoscopic features suggestive of deep submucosal invasion include converging folds, irregular surface pattern, and ulceration in a large gastric mass*

Endometrial Carcinoma – Uterine Neoplasms ‡ [8,20,35]

- Used in combination with carboplatin and paclitaxel, followed by single agent maintenance therapy; **AND**
- Patient has uterine serous carcinoma OR carcinosarcoma **Ω**; **AND**
  - Patient has stage III/IV disease; **OR**
  - Patient has recurrent disease and has not received prior trastuzumab therapy; **AND**
    - Used as first-line therapy; **AND**
      - Patient does not have isolated metastases; **OR**
    - Used as subsequent therapy

Colorectal Cancer (CRC) ‡ [8,10,32,21e,22e]

- Patient has RAS and BRAF wild-type (WT) disease; **AND**
- Used in combination with pertuzumab, lapatinib, or tucatinib; **AND**
  - Used as initial treatment for unresectable metastatic disease and previous FOLFOX or CapeOX within the past 12 months **Ω**; **AND**
    - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
  - Used as primary treatment for unresectable (or medically inoperable) or metastatic disease if intensive therapy is not recommended **Ω**; **AND**
    - Patient has not previously received HER2-directed therapy; **AND**
      - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
      - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
        - Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy; **OR**
  - Used as primary treatment for T3, N Any; T1-2, N1-2; T4, N Any; or locally unresectable (or medically inoperable) <u>rectal</u> cancer if intensive therapy is not recommended **Ω**; **AND**

- Used if resection is contraindicated following total neoadjuvant therapy; **AND**
  - Patient has proficient mismatch repair/microsatellite-stable (pMMR/MSS) disease; **OR**
  - Patient has deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
    - Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy; **OR**
- Used if resection is contraindicated following neoadjuvant/definitive immunotherapy; **AND**
  - Patient has deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) disease; **OR**

- Used as subsequent therapy for progression of advanced or metastatic disease; **AND**
  - Patient has not previously received HER2-directed therapy; **AND**
    - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
    - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
      - Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy

Appendiceal Adenocarcinoma – Colon Cancer ‡ Ω [8,10]

- Patient has RAS and BRAF wild-type (WT) disease; **AND**
- Used in combination with pertuzumab, lapatinib, or tucatinib; **AND**
- Patient has not previously received HER2-targeted therapy; **AND**
- Used for one of the following:
  - Used as initial therapy for advanced or metastatic disease if intensive therapy is not recommended; **OR**
  - Used as subsequent therapy for progression of advanced or metastatic disease; **AND**
- Used in one of the following:
  - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
  - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation; **AND**
    - Patient is not eligible for or has progressed on checkpoint inhibitor immunotherapy

Head and Neck Cancers ‡ [8,40-43]

- Patient has salivary gland tumors; **AND**
- Used as a single agent **Ω** OR in combination with either docetaxel or pertuzumab; **AND**
- Patient has recurrent disease with one of the following:
  - Distant metastases
  - Unresectable locoregional recurrence with prior radiation therapy (RT)
  - Unresectable second primary with prior RT

Biliary Tract Cancers (Gallbladder Cancer or Intra-/Extra-Hepatic Cholangiocarcinoma) ‡ [8,46,47,52,44e]

- Used as subsequent treatment for progression on or after systemic treatment for unresectable **Ω**, resected gross residual (R2) **Ω**, or metastatic disease; **AND**
- Used in combination with pertuzumab or tucatinib

*HER2-positive overexpression criteria
Breast, CNS, Uterine, and Head and Neck Cancer: [9,11]

• Immunohistochemistry (IHC) assay 3+; **OR**
• Dual-probe in situ hybridization (ISH) assay HER2/CEP17 ratio ≥ 2.0 AND average HER2 copy number ≥ 4.0 signals/cell; **OR**
• Dual-probe in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following:
  ○ HER2/CEP17 ratio ≥ 2.0 AND average HER2 copy number < 4.0 signals/cell AND concurrent IHC 3+; **OR**
  ○ HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 6.0 signals/cell AND concurrent IHC 2+ or 3+; **OR**
  ○ HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent IHC 3+

Biliary Tract Cancer [9,11,47]

• Immunohistochemistry (IHC) assay 3+; **OR**
• Dual-probe in situ hybridization (ISH) assay HER2/CEP17 ratio ≥ 2.0 AND average HER2 copy number ≥ 4.0 signals/cell; **OR**
• Dual-probe in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following:
  ○ HER2/CEP17 ratio ≥ 2.0 AND average HER2 copy number < 4.0 signals/cell AND concurrent IHC 3+; **OR**
  ○ HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 6.0 signals/cell AND concurrent IHC 2+ or 3+; **OR**

○ HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent IHC 3+; **OR** • Next-generation sequencing (NGS) panel HER2 amplification
Gastric, Esophageal, and Esophagogastric Junction Cancer: [33,34]
• Immunohistochemistry (IHC) assay 3+; **OR** • Fluorescence in situ hybridization (FISH) or in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following: ○ HER2/CEP17 ratio ≥ 2.0 AND concurrent IHC 2+; **OR** ○ Average HER2 copy number ≥ 6.0 signals/cell AND concurrent IHC 2+
Colorectal Cancer and Appendiceal Adenocarcinoma: [10,32]
• Immunohistochemistry (IHC) assay 3+; **OR** • Fluorescence in situ hybridization (FISH) HER2/CEP17 ratio ≥ 2 AND concurrent IHC 2+; **OR** • Next-generation sequencing (NGS) panel HER2 amplification

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

❖ *If confirmed using an immunotherapy assay-http://www.fda.gov/companiondiagnostics*

Ω *Please note that the supporting data for this indication has been assessed and deemed to be of insufficient quality based on the review conducted for the Enhanced Oncology Value (EOV) program. However, due to the absence of viable alternative treatment options, this indication will be retained in our policy and evaluated on a case-by-case basis.*

† FDA Approved Indication(s); **‡** Compendia Recommended Indication(s); **Φ** Orphan Drug

IV. Renewal Criteria [1-7]

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Duration of authorization has not been exceeded (refer to Section I); **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: cardiomyopathy (e.g., left ventricular cardiac dysfunction, arrhythmias, cardiac failure, etc.), pulmonary toxicity (e.g., dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, etc.), severe or febrile neutropenia, severe infusion-related reactions, etc.; **AND**
- Left ventricular ejection fraction (LVEF) obtained within the previous 3 months as follows:
    - LVEF is within the institutional normal limits, and has not had an absolute decrease of ≥ 16% from pre-treatment baseline; **OR**
    - LVEF is below the institutional lower limits of normal, and has not had an absolute decrease of ≥ 10% from pre-treatment baseline

V. Dosage/Administration [1-9,19,20,30,32-34,41-43,46,50,52-53]

Indication	Dose
Breast Cancer	**Neoadjuvant/Preoperative or Adjuvant Therapy** In Combination With Chemotherapy Loading dose: 4 mg/kg intravenously x 1 for every 7-day dosing schedule Maintenance dose: 2 mg/kg intravenously every 7 days for up to 18 weeks. - One week following the last weekly dose of trastuzumab, administer 6 mg/kg intravenously every 21 days. **OR** Loading dose: 8 mg/kg intravenously x 1 for every 21-day dosing schedule Maintenance dose: 6 mg/kg intravenously every 21 days Single-Agent Therapy (following chemotherapy) Loading dose: 8 mg/kg intravenously x 1 for every 21-day dosing schedule Maintenance dose: 6 mg/kg intravenously every 21 days *Note: Use for neoadjuvant/preoperative and adjuvant treatment is limited to a total of 52 weeks of treatment.* **Recurrent, Unresectable, Metastatic Disease OR Inflammatory breast cancer (alone or in combination with chemotherapy)** Loading dose: 4 mg/kg intravenously x 1 for every 7-day dosing schedule Maintenance dose: 2 mg/kg intravenously every 7 days **OR** Loading dose: 8 mg/kg intravenously x 1 for every 21-day dosing schedule Maintenance dose: 6 mg/kg intravenously every 21 days *Note: Treat until disease progression or intolerable toxicity.*
Gastric, Esophageal, and Esophagogastric Junction Cancers	Loading dose: 8 mg/kg intravenously x 1 for every 21-day dosing schedule Maintenance dose: 6 mg/kg intravenously every 21 days **OR**

	Loading dose: 6 mg/kg intravenously x 1 for every 14-day dosing schedule Maintenance dose: 4 mg/kg intravenously every 14 days *Note: Treat until disease progression or intolerable toxicity.*
Colorectal Cancer & Appendiceal Adenocarcinoma	Loading dose: 8 mg/kg intravenously x 1 for every 21-day dosing schedule Maintenance dose: 6 mg/kg intravenously every 21 days **OR** Loading dose: 4 mg/kg intravenously x 1 for every 7-day dosing schedule Maintenance dose: 2 mg/kg intravenously every 7 days *Note: Treat until disease progression or intolerable toxicity.*
CNS Cancer	**Leptomeningeal Metastases from Breast Cancer** Escalating doses up to 150 mg intrathecally or intraventricularly weekly* **Dosing is highly variable and should be individualized*. **Limited or Extensive Brain Metastases from Breast Cancer** Combination Therapy with capecitabine and tucatinib –Administer an initial dose at 8 mg/kg intravenously followed by 6 mg/kg intravenously every 21 days *Note: Treat until disease progression or intolerable toxicity.*
All other indications	Loading dose: 8 mg/kg intravenously x 1 for every 21-day dosing schedule Maintenance dose: 6 mg/kg intravenously every 21 days *Note: Treat until disease progression or intolerable toxicity.*

VI. Billing Code/Availability Information

Brand Name	HCPCS	HCPCS Description	1 BU	Vial Size & Type	NDCs
Herceptin	J9355	Injection, trastuzumab, excludes biosimilar, 10 mg	10 mg	150 mg SDV	50242-0132-xx
				420 mg MDV (*discontinued*)	50242-0333-xx (*discontinued*)
Ogivri	Q5114	Injection, trastuzumab-dkst, biosimilar, (ogivri), 10 mg	10 mg	150 mg SDV	83257-0001-xx
				420 mg MDV (with diluent)	83257-0004-xx
				420 mg MDV (no diluent)	83257-0003-xx
Kanjinti	Q5117	Injection, trastuzumab-anns, biosimilar, (kanjinti), 10 mg	10 mg	150 mg SDV	55513-0141-xx
				420 mg MDV (with diluent)	55513-0164-xx
				420 mg MDV (no diluent)	55513-0132-xx
Trazimera	Q5116	Injection, trastuzumab-qyyp, biosimilar, (trazimera), 10 mg	10 mg	150 mg SDV	00069-0308-xx
				420 mg MDV	00069-0305-xx
Herzuma	Q5113	Injection, trastuzumab-pkrb, biosimilar, (herzuma), 10 mg	10 mg	150 mg SDV	63459-0303-xx
				420 mg MDV	63459-0305-xx

Brand Name	HCPCS	HCPCS Description	1 BU	Vial Size & Type	NDCs
Ontruzant	Q5112	Injection, trastuzumab-dttb, biosimilar, (ontruzant), 10 mg	10 mg	150 mg SDV	78206-0147-xx
				420 mg MDV	78206-0148-xx
Hercessi	Q5146 *(Effective 01/01/2025)*	Injection, trastuzumab-strf (hercessi), biosimilar, 10 mg	10 mg	150 mg SDV	69448-0015-xx
				420 mg MDV	69448-0016-xx
Hercessi	J9999 *(Discontinue use on 01/01/2025)*	Not otherwise classified, antineoplastic	n/a	150 mg SDV	69448-0015-xx
				420 mg MDV	69448-0016-xx

Notes:
- Herceptin and Hercessi are only available as a single-dose vial; therefore, the JW modifier is allowed
- Ogivri, Kanjinti, Trazimera, Herzuma, & Ontruzant are available as both single-dose and multi-dose vials. Approvals are based upon use of the MDV; therefore, the JW modifier is not allowed

VII. References (STANDARD)

1. Herceptin [package insert]. South San Francisco, CA; Genentech, Inc; June 2024. Accessed December 2024.
2. Ogivri [package insert]. Cambridge, MA; Biocon Biologics; August 2024. Accessed December 2024.
3. Kanjinti [package insert]. Thousand Oaks, CA; Amgen, Inc; October 2022. Accessed December 2024.
4. Trazimera [package insert]. Cork, Ireland; Pfizer Ireland, Inc; November 2020. Accessed December 2024.
5. Herzuma [package insert]. Yeonsu-gu, Incheon, Republic of Korea; Celltrion, Inc; May 2019. Accessed December 2024.
6. Ontruzant [package insert]. Yeonsu-gu, Incheon, Republic of Korea; Samsung Bioepsis; June 2021. Accessed December 2024.
7. Hercessi [package insert]. Raleigh, NC; Accord BioPharma Inc.; September 2024. Accessed December 2024.
8. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) trastuzumab. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed December 2024.
9. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer, Version 6.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are

trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.

10. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer, Version 5.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.
11. Wolff AC, Hammond EH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36:2105-2122.
12. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353:1673-1684 and supplementary appendix.
13. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353:1659-1672.
14. Cameron D, Piccart-Gebhart MJ, Gelber RD et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017 Mar 25;389(10075):1195-1205.
15. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002 Feb 1;20(3):719-26.
16. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol. 2008 Apr 1;26(10):1642-9.
17. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer.
18. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28;376(9742):687-97. J Clin Oncol. 2006 Jun 20;24(18):2786-92.
19. Zagouri F, Sergentanis TN, Bartsch R, et al. Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis. Breast Cancer Res Treat 2013; 139:13-22.

20. Fader AN, Roque DM, Siegel E, et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu. J Clin Oncol. 2018 Jul 10;36(20):2044-2051. doi: 10.1200/JCO.2017.76.5966. Epub 2018 Mar 27.
21. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. Clin Oncol. 2018 Feb 20;36(6):536-542.
22. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. J Oncol Pract. 2018 Mar;14(3):e130-e136.
23. Hematology/Oncology Pharmacy Association (2019). *Intravenous Cancer Drug Waste Issue Brief*. Retrieved from https://www.hoparx.org/about-us/advocacy-awareness/issue-briefs/
24. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016 Feb 29;352:i788.
25. von Minckwitz G, Colleoni M, Kolberg HC, et al. Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2018;19:987-998.
26. Rugo HS, Barve A, Waller CF, et al. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with ERBB2 (HER2)-positive metastatic breast cancer: a randomized clinical trial. JAMA. 2017;317:37–47.
27. Pivot X, Bondarenko I, Nowecki Z, et al. Phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early breast cancer. J Clin Oncol. 2018;36:968-974.
28. Pegram MD, Bondarenko I, Zorzetto MMC, et al. PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study. Br J Cancer. 2019;120:172-182.
29. Esteva FJ, Baranau YV, Baryash V, et al. Efficacy and safety of CT-P6 versus reference trastuzumab in HER2-positive early breast cancer: updated results of a randomised phase 3 trial. Cancer Chemother Pharmacol. 2019 Oct;84(4):839-847.
30. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med.2020;382:597-609.
31. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers, Version 3.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.

32. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer, Version 4.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.
33. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer, Version 4.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.
34. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Esophageal and Esophagogastric Junction Cancers, Version 4.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.
35. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms, Version 3.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.
36. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-3752.
37. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-1283.
38. Eiermann W; International Herceptin Study Group. Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: pivotal trial data. Ann Oncol. 2001;12 Suppl 1:S57-S62.
39. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol. 1999;17(9):2639-2648.
40. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancers, Version 1.2025. National Comprehensive Cancer

Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.

41. Thorpe L, Schrock A, Erlich R, et al. Significant and durable clinical benefit from trastuzumab in 2 patients with HER2-amplified salivary gland cancer and a review of the literature. Head Neck 2017 Mar;39(3):E40-E44. doi: 10.1002/hed.24634. Epub 2016 Dec 22.
42. Kurzrock R, Bowles D, Kang H, et al. Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: results from MyPathway, a phase IIa multiple basket study. Annals of Oncology, Volume 31, Issue 3, 412 – 421
43. Takahashi H, Tada Y, Saotome T, et al. Phase II Trial of Trastuzumab and Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Salivary Duct Carcinoma. J Clin Oncol 2019 Jan 10;37(2):125-134. doi: 10.1200/JCO.18.00545. Epub 2018 Nov 19.
44. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. J Clin Oncol. 2021 May 1;39(13):1485-1505. doi: 10.1200/JCO.20.03399. Epub 2021 Jan 28. PMID: 33507815; PMCID: PMC8274745.
45. Gennari A, André F, Barrios CH, et al.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021 Dec;32(12):1475-1495. doi: 10.1016/j.annonc.2021.09.019. Epub 2021 Oct 19. PMID: 34678411.
46. Javle M, Borad MJ, Azad NS, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2021 Sep;22(9):1290-1300. doi: 10.1016/S1470-2045(21)00336-3. Epub 2021 Jul 30.
47. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Biliary Tract Cancers, Version 5.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.
48. Buza N, English DP, Santin AD, Hui P. Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice. Mod Pathol. 2013 Dec;26(12):1605-12. doi: 10.1038/modpathol.2013.113.
49. Bartley AN, Washington MK, Colasacco C, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol. 2017 Feb;35(4):446-464. doi: 10.1200/JCO.2016.69.4836.

50. Lin NU, Pegram M, Sahebjam S, et al. Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary Analysis of a Phase II Study. J Clin Oncol. 2021 Aug 20;39(24):2667-2675. doi: 10.1200/JCO.20.02822.
51. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet 2023;402:2197-2208.
52. Nakamura Y, Mizuno N, Sunakawa Y, et al. Tucatinib and Trastuzumab for Previously Treated Human Epidermal Growth Factor Receptor 2-Positive Metastatic Biliary Tract Cancer (SGNTUC-019): A Phase II Basket Study. J Clin Oncol. 2023 Dec 20;41(36):5569-5578. doi: 10.1200/JCO.23.00606. Epub 2023 Sep 26.
53. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Intrathecal Trastuzumab: Central Nervous System Cancers Chemotherapy Order Template, CNS30. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed December 2024.
54. First Coast Service Options, Inc. Local Coverage Article: Billing and Coding: Trastuzumab - Trastuzumab Biologics (A56660). Centers for Medicare & Medicaid Services, Inc. Updated on 10/08/2021 with effective date of 10/01/2021. Accessed December 2024.

VIII. References (ENHANCED)

1e. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010 Jan 30;375(9712):377-84.
2e. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012 Jan;13(1):25-32.
3e. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016 Jun;17(6):791-800.
4e. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013 Sep;24(9):2278-84.

5e. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131.

6e. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011;29(25):3366-73.

7e. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006 Feb 23;354(8):809-20.

8e. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005 Oct 20;353(16):1659-72.

9e. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007 Jan 6;369(9555):29-36.

10e. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrazole versus anastrazole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol. 2009 Nov 20;27(33):5529-37.

11e. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2011;366(2):109-19.

12e. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-34.

13e. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar 15;344(11):783-92.

14e. Andersson M, Lidbrink E, Bjerre K, et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol. 2011 Jan 20;29(3):264-71.

15e. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.

16e. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012 Jul 20;30(21):2585-92.

17e. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol. 2010;28(7):1138-44.

18e. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2009 Nov 20;27(33):5538-46.

19e. Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist. 2010;15(9):924-34.

20e. Johnston SRD, Hegg R, Im SA, et al. Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade With Lapatinib Plus Trastuzumab in Combination With an Aromatase Inhibitor in Postmenopausal Women With HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: ALTERNATIVE. J Clin Oncol. 2018 Mar 10;36(8):741-748. doi: 10.1200/JCO.2017.74.7824.

21e. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2019 Apr;20(4):518-530. doi: 10.1016/S1470-2045(18)30904-5.

22e. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016 Jun;17(6):738-746. doi: 10.1016/S1470-2045(16)00150-9.

23e. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013;14(1):64-71. doi:10.1016/S1470-2045(12)70432-1.

24e. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. J Clin Oncol. 2019;37(13):1081-1089. doi:10.1200/JCO.18.01511.

25e. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2020;382(7):610-621. doi:10.1056/NEJMoa1914510.

26e. Jhaveri KL, Wang XV, Makker V, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. Ann Oncol. 2019 Nov 1;30(11):1821-1830. doi: 10.1093/annonc/mdz291.

27e. Saura C, Oliveira M, Feng YH, et al. NALA Investigators. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol. 2020 Sep 20;38(27):3138-3149. doi: 10.1200/JCO.20.00147. Epub 2020 Jul 17.

28e. Rugo HS, Im SA, Cardoso F,et al. SOPHIA Study Group. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3

Randomized Clinical Trial. JAMA Oncol. 2021 Apr 1;7(4):573-584. doi: 10.1001/jamaoncol.2020.7932.

29e. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial. Ann Oncol. 2020 Oct;31(10):1350-1358. doi: 10.1016/j.annonc.2020.06.020. Epub 2020 Jul 5.

30e. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol. 2014 May;15(6):640-7. doi: 10.1016/S1470-2045(14)70080-4. Epub 2014 Mar 20. Erratum in: Lancet Oncol. 2018 Dec;19(12):e667. PMID: 24657003.

31e. Taghian A. and Merajver S. (2020). Inflammatory breast cancer: Clinical features and treatment. In D.F. Hayes, L.J. Pierce, and A.B. Chagpar (Eds.), UptoDate. Available from: https://www.uptodate.com/contents/inflammatory-breast-cancer-clinical-features-and-treatment?search=inflammatory%20breast%20cancer&source=search_result&selectedTitle=1~48&usage_type=default&display_rank=1#H4025803376.

32e. Sikov W.M. (2021). Neoadjuvant therapy for patients with HER2-positive breast cancer. In H.J. Burstein (Eds.), UptoDate. Available from: https://www.uptodate.com/contents/neoadjuvant-therapy-for-patients-with-her2-positive-breast-cancer?sectionName=TIMING%20OF%20HER2-DIRECTED%20AGENTS&search=inflammatory%20breast%20cancer%20treatment&topicRef=768&anchor=H1845125338&source=see_link#H1845125338.

33e. Burstein H.J. (2021). Adjuvant systemic therapy for HER2-positive breast cancer. In D.F. Hayes (Eds.), UptoDate. Available from: https://www.uptodate.com/contents/adjuvant-systemic-therapy-for-her2-positive-breast-cancer?sectionName=Non-anthracycline-based%20therapy&search=inflammatory%20breast%20cancer&topicRef=106774&anchor=H1352264107&source=see_link#H1237051481.

34e. Rivera F, Romero C, Jimenez-Fonseca P, et al. Phase II study to evaluate the efficacy of Trastuzumab in combination with Capecitabine and Oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial [published correction appears in Cancer Chemother Pharmacol. 2019 Dec;84(6):1365]. Cancer Chemother Pharmacol. 2019;83(6):1175-1181. doi:10.1007/s00280-019-03820-7.

35e. Chung HC, Bang YJ, S Fuchs C, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. Future Oncol. 2021;17(5):491-501. doi:10.2217/fon-2020-0737.

36e. Siena S, Di Bartolomeo M, Raghav KPS, et al. A phase II, multicenter, open-label study of trastuzumab deruxtecan in patients with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01. J Clin Oncol 2020;38(suppl; abstr 4000).

37e. Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and Trastuzumab in Heavily Pretreated Metastatic Breast Cancer. J Clin Oncol 2007;25:3853-3858.

38e. Jerusalem G, Park YH, Yamashita T, et al. Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: A subgroup analysis of the DESTINY-Breast01 trial. J Clin Oncol 2021;39(15_suppl):526.

39e. Lin NU, Pegram M, Sahebjam S, et al. Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary Analysis of a Phase II Study. J Clin Oncol. 2021 Aug 20;39(24):2667-2675. doi: 10.1200/JCO.20.02822. Epub 2021 May 4.

40e. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol. 2009 Apr 20;27(12):1999-2006. doi: 10.1200/JCO.2008.19.6618. Epub 2009 Mar 16.

41e. Lee YR, Huh SJ, Lee DH, et al. Phase II Study of Vinorelbine Plus Trastuzumab in HER2 Overexpressing Metastatic Breast Cancer Pretreated with Anthracyclines and Taxanes. J Breast Cancer. 2011;14(2):140-146. doi:10.4048/jbc.2011.14.2.140.

42e. Strickler JH, Cercek A, Siena S, et al. Additional analyses of MOUNTAINEER: A phase II study of tucatinib and trastuzumab for HER2-positive mCRC [abstract]. Annals of Oncology 2022;33:S808-S869.

43e. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. The Lancet. 2022;0(0). doi:https://doi.org/10.1016/S0140-6736(22)02420-5

44e. Nakamura Y, Mizuno N, Sunakawa Y, et al. Tucatinib and Trastuzumab for Previously Treated Human Epidermal Growth Factor Receptor 2–Positive Metastatic Biliary Tract Cancer (SGNTUC-019): A Phase II Basket Study. Journal of clinical oncology. 2023;41(36):5569-5578. doi:https://doi.org/10.1200/jco.23.00606

45e. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. Published online October 23, 2023:101200JCO2302005. doi:https://doi.org/10.1200/JCO.23.02005

46e. Haddad R, Colevas AD, Krane JF, et al. Herceptin in patients with advanced or metastatic salivary gland carcinomas. A phase II study. Oral Oncol. 2003 Oct;39(7):724-7.

47e. Prime Therapeutics Management. Trastuzumab IV Clinical Literature Review Analysis. Last updated December 2024. Accessed December 2024.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C06.9	Malignant neoplasm of mouth, unspecified
C07	Malignant neoplasm of parotid gland
C08.0	Malignant neoplasm of submandibular gland
C08.1	Malignant neoplasm of sublingual gland
C08.9	Malignant neoplasm of major salivary gland, unspecified
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of the lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C18.0	Malignant neoplasm of cecum
C18.2	Malignant neoplasm of ascending colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C50.011	Malignant neoplasm of nipple and areola, right female breast

ICD-10	ICD-10 Description
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right female breast
C50.022	Malignant neoplasm of nipple and areola, left female breast
C50.029	Malignant neoplasm of nipple and areola, unspecified female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast

ICD-10	ICD-10 Description
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
C79.32	Secondary malignant neoplasm of cerebral meninges
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung

ICD-10	ICD-10 Description
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.3	Personal history of malignant neoplasm of breast
Z85.42	Personal history of malignant neoplasm of other parts of uterus

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC