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

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I. Length of Authorization [1-6]

Coverage is provided for six months and may be renewed.

- Use in the neo-adjuvant and adjuvant setting is limited to a total of 52 weeks of treatment.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Herceptin 150 mg single-dose vial: 7 vials every 21 days
- Herceptin 420 mg multiple-dose vial: 3 vials every 21 days
- Ogivri 150 mg single-dose vial: 7 vials every 21 days
- Ogivri 420 mg multiple-dose vial: 3 vials every 21 days
- Kanjinti 150 mg single-dose vial: 7 vials every 21 days
- Kanjinti 420 mg multiple-dose vial: 3 vials every 21 days
- Trazimera 150 mg single-dose vial: 7 vials every 21 days
- Trazimera 420 mg multiple-dose vial: 3 vials every 21 days
- Herzuma 150 mg single-dose vial: 7 vials every 21 days
- Herzuma 420 mg multiple-dose vial: 3 vials every 21 days
- Ontruzant 150 mg single-dose vial: 7 vials every 21 days
- Ontruzant 420 mg multiple-dose vial: 3 vials every 21 days

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

Breast Cancer & Colorectal Cancer

	Load (billable units)	Maintenance (billable units)
7-day dosing schedule	45	30
21-day dosing schedule	90	75

Gastric/Esophageal/Gastro-esophageal Junction Cancers

	Load (billable units)	Maintenance (billable units)
7-day dosing schedule	45	30
14-day dosing schedule	75	45

CNS Cancer (Limited/Extensive brain metastases) & Uterine Cancer

- 90 billable units, followed by 75 billable units every 21 days

III. Initial Approval Criteria [1-6]

Coverage is provided in the following conditions:

Requests for Herceptin® (J9355), Herzuma® (Q5113), or Ontruzant® (Q5112):

Patient must have a contraindication or intolerance to all of the following prior to consideration of Herceptin® (J9355), Herzuma® (Q5113), or Ontruzant® (Q5112): trastuzumab-anns (Kanjinti™ [Q5117]), trastuzumab-dkst (Ogivri™ [Q5114]), and trastuzumab-qyyp (Trazimera™ [Q5116]); **AND**

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

Universal Criteria [1-6]

- 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**
- Therapy will not be substituted with or for ado-trastuzumab emtansine (Kadcyla) or fam-trastuzumab deruxtecan-nxki (Enhertu); **AND**
- Will not be used in combination with trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or pertuzumab/trastuzumab and hyaluronidase-zzxf (Phesgo); **AND**

Breast Cancer † ‡ [1-8,10-16,35-38,10e,11e,13e,14e,16e,17e,19e,20e]

- Used as adjuvant therapy; **AND**
  - Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) †; **OR**
  - Used as a single agent following chemotherapy; **OR**
  - Used in combination with pertuzumab for node positive (N1-N3) disease; **OR**
- Used as neoadjuvant or preoperative therapy for locally advanced or node positive disease; **AND**
  - Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) with or without pertuzumab; **OR**
- Used for recurrent or metastatic disease; **AND**

- Used as a single agent in patients who have received one or more prior treatments for metastatic disease †; **OR**
- Used as first-line therapy in combination with paclitaxel †; **OR**
- Used in combination with endocrine therapy (e.g., tamoxifen, fulvestrant, or aromatase inhibition with or without lapatinib) in patients with hormone-receptor positive disease; **AND**
  - Patient is post-menopausal; **OR**
  - Patient is pre-menopausal and is treated with ovarian ablation/suppression; **OR**
  - Patient is a male receiving concomitant suppression of testicular steroidogenesis; **OR**
- Used in combination with one of the following:
  - cytotoxic chemotherapy
  - lapatinib (without cytotoxic therapy) after prior anti-HER2 directed therapy for metastatic disease
  - capecitabine plus tucatinib *(includes use in advanced unresectable disease)* after prior HER2-targeted therapy with trastuzumab, pertuzumab, AND ado-trastuzumab emtansine
  - pertuzumab and a taxane (e.g., docetaxel, paclitaxel) as first-line therapy
  - pertuzumab with or without cytotoxic therapy as one-line of therapy beyond first-line therapy in patients who were previously treated with trastuzumab without pertuzumab

Central Nervous System Cancer ‡ [7,18,29,30]

- Patient has limited or extensive brain metastases from breast cancer; **AND**
  - Used in combination with capecitabine and tucatinib; **AND**
  - Patient previously received trastuzumab, pertuzumab, AND ado-trastuzumab; **AND**
    - Used as primary treatment in patients with small asymptomatic brain metastases; **OR**
    - Used for relapsed disease in patients with limited brain metastases who are systemically stable or have other reasonable systemic treatment options; **OR**
    - Used for recurrent limited brain metastases; **OR**
    - Used for recurrent disease in patients with extensive brain metastases who are systemically stable or have other reasonable systemic treatment options

Gastric, Esophageal and Esophagogastric Junction Cancers † Φ [1-7,17,32,33]

- Used in combination with cisplatin and 5-FU or capecitabine for first-line therapy; **AND**
- Patient has unresectable locally advanced, recurrent, or metastatic adenocarcinoma

Uterine Cancer (Endometrial Carcinoma) ‡ [7,19,34]

- Used in combination with carboplatin and paclitaxel; **AND**
- Patient has advanced (stage III/IV) or recurrent uterine serous carcinoma

Colorectal Adenocarcinoma ‡ [7,9,31,21e,22e]

- Used in combination with pertuzumab or lapatinib in patients who have not previously received HER2-targeted therapy; **AND**
- Patient has RAS and BRAF wild-type (WT) disease; **AND**
    - Used as subsequent therapy for progression of advanced or metastatic disease after at least one prior line of treatment in the advanced or metastatic disease setting

Head and Neck Cancer ‡ [7,39-42]

- Patient has salivary gland tumors; **AND**
- Patient has unresectable, recurrent, or metastatic disease; **AND**
    - Used in combination with pertuzumab; **OR**
    - Used in combination with docetaxel

*HER2-positive overexpression criteria: [8,10]

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+

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*

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

IV. Renewal Criteria [1-9]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **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 the following: cardiotoxicity (e.g., left ventricular dysfunction, cardiomyopathy, etc.), pulmonary toxicity (e.g., dyspnea, interstitial pneumonitis, etc.), neutropenia; infusion-related reactions, etc.; **AND**
    - LVEF is within the institutional normal limits, but has not had an absolute decrease of ≥ 16% from pre-treatment baseline (LVEF results must be within the previous 3 months); **OR**
    - LVEF is below the institutional lower limits of normal, but has not had an absolute decrease of ≥ 10% from pre-treatment baseline (LVEF results must be within the previous 3 months); **AND**
- Use for neoadjuvant and adjuvant breast cancer treatment is limited to a total of 52 weeks of therapy

V. Dosage/Administration [1-9,18,29]

Indication	Dose
Breast Cancer	**Neo-adjuvant/Adjuvant Therapy** Combination Therapy –Administer an initial dose of 4 mg/kg intravenously followed by 2 mg/kg intravenously weekly during chemotherapy for up to 18 weeks. –One week following the last weekly dose of trastuzumab, administer 6 mg/kg intravenously every three weeks. Single-Agent Therapy (following anthracycline therapy) –Administer an initial dose at 8 mg/kg intravenously, followed by subsequent doses at 6 mg/kg intravenously every three weeks. *Note: Therapy should not exceed a total of 52 weeks of treatment.* **Recurrent or Metastatic Disease (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 every 21 days *Note: Treat until disease progression or intolerable toxicity.*
Gastric, Esophageal and	Loading dose: 8 mg/kg intravenously x 1 for every 21-day dosing schedule Maintenance dose: 6 mg/kg intravenously every 21 days

Esophagogastric Junction Cancers	**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	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 Metastases from Breast Cancer	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.*
Uterine Cancer	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.*
Head and Neck Cancer	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

HCPCS Code :

- J9355 - Injection, trastuzumab, excludes biosimilar, 10 mg; 1 bu = 10mg
- Q5114 – Injection, Trastuzumab-dkst, biosimilar, (Ogivri), 10 mg; 1 bu = 10 mg
- Q5117 - Injection, trastuzumab-anns, biosimilar, (Kanjinti), 10 mg: 1 bu = 10 mg
- Q5116 – Injection, trastuzumab-qyyp, biosimilar, (Trazimera), 10 mg; 1 bu = 10 mg
- Q5113 – Injection, Trastuzumab-pkrb, biosimilar, (Herzuma), 10 mg; 1 bu = 10 mg
- Q5112 – Injection, Trastuzumab-dttb, biosimilar, (Ontruzant), 10 mg; 1 bu = 10 mg

NDC(s):

- Herceptin 150 mg single-dose vial; powder for injection: 50242-0132-xx
- Herceptin 420 mg multiple-dose vial; powder for injection: 50242-0333-xx*
- Ogivri 150 mg single-dose vial; powder for injection: 67457-0991-xx
- Ogivri 420 mg multiple-dose vial; powder for injection: 67457-0847-xx
- Kanjinti 150 mg single-dose vial powder for injection: 55513-0141-xx
- Kanjinti 420 mg multiple-dose vial; powder for injection: 55513-0132-xx
- Trazimera 150 mg single-dose vial; lyophilized powder for injection: 00069-0308-xx
- Trazimera 420 mg multiple-dose vial; lyophilized powder for injection: 00069-0305-xx
- Herzuma 150 mg single-dose vial; powder for injection: 63459-0303-xx
- Herzuma 420 mg multiple-dose vial: powder for injection: 63459-0305-xx

- Ontruzant 150 mg single-dose vial; powder for injection: 00006-5033-xx
- Ontruzant 420 mg multiple-dose vial; powder for injection: 00006-5034-xx
  **Note: Not commercially available*

VII. References (STANDARD)

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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

ICD-10	ICD-10 Description
C17.0	Malignant neoplasm duodenum
C17.1	Malignant neoplasm jejunum
C17.2	Malignant neoplasm ileum
C17.8	Malignant neoplasm of overlapping sites of small intestines
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
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
C50.011	Malignant neoplasm of nipple and areola, right female breast
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

ICD-10	ICD-10 Description
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
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

ICD-10	ICD-10 Description
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
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
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
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.3	Personal history of malignant neoplasm of breast

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

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 Determination (NCD), Local Coverage Articles (LCAs), and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

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

Jurisdiction(s): N(9)	**NCD/LCD/LCA Document (s):** A56660
https://www.cms.gov/medicare-coverage-database/search/document-id-search-results.aspx?Date=10/30/2019&DocID=A56660&bc=hAAAAAAAAAAA&	

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 (WPS)
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 (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
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

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; RFS = recurrence-free survival

HER2-Positive Breast Cancer

Neoadjuvant treatment							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trastuzumab+ neoadjuvant anthracycline- and taxane-based chemotherapy	2A preferred or 2A depending on the regimen	Yes	Phase 2 (NOAH), randomized	N/A	EFS	Treatment naive	• Trastuzumab significantly improved EFS in patients with HER2-positive breast cancer. • Addition of trastuzumab did not increase cardiotoxicity.
Docetaxel + trastuzumab + pertuzumab (THP)	2A preferred	Yes (with trastuzumab and chemotherapy for locally advanced, inflammatory, or early stage breast cancer [either greater than 2 cm in diameter or node positive])	Phase 2 (NeoSphere), open-label 5-year analysis	Trastuzumab+ docetaxel Pertuzumab+ docetaxel Trastuzumab+ pertuzumab	pCR	Treatment naïve Node-positive or tumor > 2 cm locally advanced or inflammatory breast cancer	• Pertuzumab+ trastuzumab + docetaxel had a higher pCR rate (46%) than those receiving docetaxel with just trastuzumab or just pertuzumab.

Docetaxel+ carboplatin+ trastuzumab+ pertuzumab (TCHP)	2A preferred	Yes (with trastuzumab and chemotherapy for locally advanced, inflammatory, or early stage breast cancer [either greater than 2 cm in diameter or node positive])	Phase 2 (TRYPHAENA), open-label	FECHP-THP (fluorouracil, epirubicin, cyclophosphamide + trastuzumab [H] + pertuzumab [P followed by docetaxel (T) +HP FEC followed by THP	Safety	Treatment naïve Node-positive or tumor > 2 cm locally advanced or inflammatory breast cancer	• Rates of cardiotoxicity was comparable between groups receiving anthracycline and slightly lower in the TCHP arm. • pCR was achieved by the majority of patients and the rates of pCR did not differ significantly between treatment arms (anthracycline and non-anthracycline regimens).
Adjuvant treatment							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Standard chemotherapy (anthracycline and non-anthracycline)+ trastuzumab+ pertuzumab	2A preferred (AC-THP or with TCH-P)	Yes for early breast cancer at high-risk of recurrence	Phase III (APHINITY), randomized, double-blind, placebo-controlled	Standard chemotherapy+ trastuzumab+ placebo	DFS	Adjuvant	• Pertuzumab improved the rate of DFS when added to trastuzumab and chemotherapy. • No treatment effect was observed in patients with node-negative disease.
Doxorubicin, cyclophosphamide followed by paclitaxel, trastuzumab (AC-TH)	2A preferred	Yes	Joint analysis of phase III studies: NSABP B-31 and NCCTG N9831	Doxorubicin, cyclophosphamide followed by paclitaxel (AC-T)	DFS	Adjuvant	• Addition of trastuzumab to adjuvant chemotherapy demonstrated a 39% improvement in OS and a 48% improvement in DFS. • Trastuzumab appeared to increase cardiac toxicities.

Docetaxel+ carboplatin+ trastuzumab (TCH)	2A preferred	Yes	Phase III (BCIRG 006), randomized	Doxorubicin, cyclophosphamide followed by paclitaxel (AC-T) or AC-T + trastuzumab (H)	DFS	Adjuvant HER2-positive, node-positive or high-risk node-negative High risk: <35 years; tumor > 2cm, ER/PR-negative, tumor grade 2 or 3	• Trastuzumab-containing regimens significantly improve DFS and OS. • TCH and AC-TH were similar in efficacy and both are superior to AC-T. • TCH was associated lower cardiotoxicity.
Trastuzumab + docetaxel or vinorelbine	2A		Phase 3 (FinHer), open-label, multicenter	Docetaxel or vinorelbine	RFS	Adjuvant	• Addition of trastuzumab was associated with a reduction in risk of recurrence. • No statistically significant difference in OS was observed.
Trastuzumab (1 year)	2A?	Yes	Phase 3 (HERA), open-label, randomized, multicenter 2-year follow up	Trastuzumab (2 years) or observation	DFS	After adjuvant therapy	• One year of treatment with trastuzumab after adjuvant chemotherapy significantly improves DFS and OS.
Recurrent or Metastatic Breast Cancer Hormone-Receptor Positive							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Trastuzumab + anastrazole	2A	No	Phase 3 (TAnDEM), randomized, open-label, multicenter	Anastrazole alone	PFS	Any line of therapy (no chemotherapy, adjuvant or metastatic setting, within 6 months)	• Trastuzumab plus anastrazole improves PFS compared to anastrazole alone • More adverse events were seen with the combination
Lapatinib + letrozole	2A	Yes	Phase 3 (EFG 30008), randomized, double-blind, controlled multi-center	Letrozole	PFS	First-line	• This trial demonstrated that a combined targeted strategy with letrozole and lapatinib significantly enhances PFS and clinical benefit rates in patients with MBC that coexpresses HR and HER2.
Trastuzumab + lapatinib + aromatase inhibitor (AI)	2A	No	Phase 3 (ALTERNATIVE), randomized	Trastuzumab + AI vs. Lapatinib + AI	PFS	Prior trastuzumab and prior endocrine therapy, either in the adjuvant or metastatic disease setting	• Dual HER2 blockade with LAP + TRAS + AI showed superior PFS benefit versus TRAS + AI in patients with HER2-positive/HR-positive MBC.
First-Line Therapy of Recurrent or Metastatic Breast Cancer							
Pertuzumab+ trastuzumab + docetaxel	1 preferred	Yes	Phase 3 (CLEOPATRA), randomized, double-blind, placebo-controlled	Docetaxel + trastuzumab+ placebo	PFS	First-line in metastatic breast cancer (patients with prior adjuvant or neoadjuvant therapy, with or without	• Pertuzumab group significantly prolonged PFS and OS.

			Second interim analysis			trastuzumab, must have an interval of at least 12 months between completion of the adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer)	
Trastuzumab + standard chemotherapy (paclitaxel or anthracycline + cyclophosphamide)	2A other	Yes	Phase 3	Standard chemotherapy (paclitaxel or anthracycline + cyclophosphamide)	TTP	First-line	• Addition of trastuzumab to chemotherapy in first-line therapy increases TTP and improves OS. • Magnitude of treatment effects were greatest in the paclitaxel subgroup.
Trastuzumab+ vinorelbine	2A other	No	Phase 3 (HERNATA), randomized	Trastuzumab+ docetaxel	TTP	First-line	• Neither arm demonstrated significant improvement in survival. • However, vinorelbine combination was better tolerated than trastuzumab+ docetaxel .
Trastuzumab+ paclitaxel	2A other	Yes	Phase 3, randomized, multicenter	Trastuzumab+ paclitaxel + carboplatin	ORR	First-line for metastatic disease (taxane not used in neoadjuvant or	• Trastuzumab+ paclitaxel + carboplatin improved ORR and PFS. • Trend toward improved OS with trastuzumab+ paclitaxel +

						adjuvant therapy)	carboplatin however, not statistically significant. • Increased rates of neutropenia was associated with TPC.
Second-Line Therapy of Recurrent or Metastatic Breast Cancer							
Ado- trastuzumab emtansine (T-DM1)	2A other	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy)	Phase 3 (EMILIA), randomized, open-label	Lapatinib+ capecitabine	PFS OS Safety	Previous treatment with trastuzumab and a taxane (in any setting) • First-line with progression within 6-months after adjuvant therapy • Second-line therapy or later for locally advanced or metastatic disease	• T-DM1 significantly prolonged PFS and OS with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane.
Trastuzumab+ lapatinib	2A other	No	Phase III (EGF104900 Study), randomized, open-label	Lapatinib monotherapy	PFS	Second-line therapy or later after one or more prior trastuzumab-containing regimens for metastatic disease	• Modest improvement (3 weeks) in PFS with lapatinib+ trastuzumab versus lapatinib alone. • A 4.5mon OS advantage with lapatinib+ trastuzumab was seen over lapatinib alone in patients with pretreated HER2-positive metastatic breast cancer.

Lapatinib+ capecitabine	2A other	Yes	Phase 3, randomized	Capecitabine alone	TTP	Second-line therapy or later after prior trastuzumab (metastatic setting) and prior treatment with an anthracycline and a taxane (metastatic or adjuvant setting)	• Lapatinib+ capecitabine demonstrated a significant benefit in TTP and a trend towards an improvement in OS compared to capecitabine alone.
Trastuzumab monotherapy	None	Yes	Phase 2	N/A	---------	Second- or third-line	• Trastuzumab administered as a single agent produces durable objective responses in women with HER2-positive metastatic breast cancer.
Trastuzumab+ pertuzumab	2A other	No (Pertuzumab + trastuzumab + docetaxel is FDA approved for patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease)	Phase 2, open-label, single-arm	N/A	ORR	After prior trastuzumab-based therapy in metastatic setting	• Pertuzumab and trastuzumab is active and well tolerated in patients with metastatic HER2-positive breast cancer who had experienced progression during prior trastuzumab therapy.

Tucatinib + trastuzumab + capecitabine	1 other	Yes	Phase 3 (HER2CLIMB), randomized	Placebo + trastuzumab + capecitabine	PFS	Previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine	• In heavily pretreated patients with HER2-positive metastatic breast cancer, including those with brain metastases, adding tucatinib to trastuzumab and capecitabine resulted in better progression-free survival and overall survival outcomes than adding placebo; the risks of diarrhea and elevated aminotransferase levels were higher with tucatinib.
Fam-trastuzumab deruxtecan-nxki	2A	Yes (after 2 or more prior anti-HER2-based regimens)	Phase 2 (DESTINY-Breast01), open-label, single-arm	N/A	ORR	≥ 2 prior therapies including T-DM1	• Trastuzumab deruxtecan showed durable antitumor activity in a pretreated patient population with HER2-positive metastatic breast cancer with an ORR 60.9% and duration of response of 14.8 months.

Central Nervous System Cancer

Leptomeningeal Metastases in Breast Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trastuzumab (intrathecal)	2A	No	Systematic review and pooled analysis	N/A	----------	----------	• Intrathecal administration of trastuzumab demonstrated to be an effective option for the treatment of HER2-positive breast cancer patients with leptomeningeal metastases
Leptomeningeal Metastases in Breast Cancer							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Tucatinib + trastuzumab + capecitabine	2A	No	Phase 3 (HER2CLIMB), randomized	Placebo + trastuzumab + capecitabine	PFS	Previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine	• In heavily pretreated patients with HER2-positive metastatic breast cancer, including those with brain metastases, adding tucatinib to trastuzumab and capecitabine resulted in better progression-free survival and overall survival outcomes than adding placebo; the risks of diarrhea and elevated aminotransferase levels were higher with tucatinib.
Capecitabine + lapatinib	2A	No	Phase 2 (LANDSCAPE), open-label	N/A	CNS response	Previously untreated	• The combination of lapatinib and capecitabine is active as first-line treatment of brain metastases from HER2-positive breast cancer with a CNS response rate of 65.9%.
Capecitabine + neratinib	2A	No	Phase 2 (TBCRC 022)	N/A	CNS ORR	Previously treated disease – lapatinib-naïve (cohort 3A) and lapatinib-treated (cohort 3B)	• Neratinib plus capecitabine is active against refractory, HER2-positive breast cancer brain metastases with CNS ORR 49% in lapatinib-naïve patients and CNS ORR 33% in lapatinib-treated patients.

Gastric Cancer and Esophagogastric Junction Cancers

HER2-Positive Metastatic Adenocarcinoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trastuzumab + cisplatin +	1	Yes	Phase 3 (ToGA), open-label, randomized,	Cisplatin + (fluorouracil	OS	First-line	• Trastuzumab in combination with chemotherapy significantly improved OS compared to chemotherapy alone

(fluorouracil or capecitabine)			controlled, prospective	or capecitabine)			• No difference in adverse events or cardiac adverse events were observed

Uterine Cancer

HER2-Positive Advanced or Recurrent Uterine Serous Carcinoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trastuzumab + carboplatin + paclitaxel	2A preferred	No	Phase II, randomized, multicenter	Carboplatin + paclitaxel	PFS	----------	• Addition of trastuzumab to carboplatin-paclitaxel increased PFS without increasing overall toxicity

Colorectal Cancer

Subsequent therapy for metastatic HER2-positive colorectal cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trastuzumab + pertuzumab	2A for HER2-amplified and RAS wild-type	No	Phase 2a multiple basket study (MyPathway) subset analysis	N/A	ORR	Subsequent therapy	• Dual HER2-targeted therapy with pertuzumab plus trastuzumab demonstrated an ORR 32% in patients with treatment-refractory HER2-positive metastatic colorectal cancer.
Trastuzumab + lapatinib	2A for HER2-amplified	No	Phase 2 (HERACLES), multi-center	N/A	----------	Subsequent therapy	• The combination of trastuzumab and lapatinib demonstrated an ORR 30% in patients with treatment-refractory KRAS

	and RAS wild-type						wild-type and HER2-positive colorectal cancer.

Head and Neck Cancer

Salivary gland tumors							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trastuzumab + pertuzumab	2A certain circumstances	No	Phase 2a (MyPathway), multiple basket, open-label, non-randomized, multi-center	N/A	ORR	Subsequent therapy (unless no first-line therapy exists)	• Overall, 9 of 15 patients with advanced salivary gland tumors experienced an objective response with trastuzumab plus pertuzumab.
Trastuzumab + docetaxel	2A certain circumstances	No	Phase 2, single-center, single-arm, open-label	N/A	ORR	All lines of therapy	• Trastuzumab plus docetaxel combination therapy demonstrated an ORR of 70.2% in patients with HER2 positive salivary gland tumors.
Trastuzumab + chemotherapy, followed by maintenance trastuzumab	2A certain circumstances	No	Case study	N/A	-----	-----	• Both patients treated with trastuzumab experienced rapid responses and continued to experience durable disease control with maintenance trastuzumab therapy.
Ado-trastuzumab	2A certain circumstances	No	Phase 2 (NCI-MATCH)	N/A	ORR	Following at least one line of standard systemic	• Treatment with ado-trastuzumab demonstrated an ORR of 5.6% with 2 out of 3 patients with salivary gland tumors experiencing a partial response.

emtansine (TDM-1)						therapy or for whom no standard therapy was available	