Perjeta® (pertuzumab)
(Intravenous)

-E-

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I. Length of Authorization [1]

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

- Use for neo-adjuvant and adjuvant breast cancer is limited to a total of 1 year of treatment [18 cycles] *(*Note: When used for recurrent or metastatic breast cancer, therapy may be continued until disease progression or unmanageable toxicity.)*

II. Dosing Limits

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

Perjeta 420 mg/14mL solution for injection:

- Loading Dose: 2 vials
- Maintenance Doses: 1 vial every 21 days

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

Loading Dose

- 840 billable units x 1 dose

Maintenance Dose

- 420 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; AND

Universal Criteria [1]

- 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 used in combination with pertuzumab/trastuzumab and hyaluronidase-zzxf (Phesgo); **AND**

Breast Cancer † [1-3,5-8,13,12e-15e]

- Used as adjuvant treatment; **AND**
  - Patient has locally advanced disease OR early stage disease at high risk of recurrence; **AND**
  - Patient has node-positive (N1-N3) disease; **AND**
  - Used in combination with a trastuzumab-based regimen; **OR**
- Used as neoadjuvant treatment for breast preservation; **AND**
  - Patient has locally advanced, inflammatory, or early stage (tumor size >2 cm in diameter or node positive) disease; **AND**
  - Used in combination with trastuzumab and chemotherapy; **OR**
- Used for recurrent or metastatic disease; **AND**
  - Used as first-line therapy in combination with trastuzumab and either paclitaxel OR docetaxel; **OR**
  - Used as second-line therapy in combination with a trastuzumab-based regimen ‡; **AND**
    - Patient was previously treated with trastuzumab and chemotherapy; **AND**
    - Patient has not previously received pertuzumab

Colorectal Cancer ‡ [2,9-12,16e]

- Used for RAS and BRAF wild-type (WT) disease in combination with trastuzumab in patients who have not previously received HER2-targeted therapy; **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 Tumors ‡ [2,14,15,20e]

- Used for salivary gland tumors; **AND**
- Used in combination with trastuzumab; **AND**
  - Used for one of the following:
    - Unresectable locally-advanced, recurrent or metastatic disease; **OR**
    - Second primary therapy with prior radiation therapy for recurrent disease

***HER2-positive overexpression criteria:[3,4]**

- 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]

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: left ventricular dysfunction, severe infusion-related reactions, hypersensitivity reactions/anaphylaxis, etc.; **AND**
- Left ventricular ejection fraction (LVEF) is >45% OR LVEF is ≥40% and absolute decrease is <10% from 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 1 year of treatment (total of 18 cycles)

V. Dosage/Administration [1,10-13,15]

Indication	Dose
Breast Cancer	Administer 840 mg intravenously x 1 dose, then 420 mg intravenously every 21 days thereafter until disease progression or unmanageable toxicity • Neoadjuvant therapy consists of 3 to 6 cycles prior to surgery • Use for neoadjuvant and adjuvant early breast cancer treatment is limited to a total of 1 year of treatment (total of 18 cycles) **Note: When used for recurrent or metastatic breast cancer, therapy may be continued until disease progression or unmanageable toxicity.*

Indication	Dose
Colorectal Cancer	Administer 840 mg intravenously x 1 dose, then 420 mg intravenously every 21 days thereafter until disease progression or unmanageable toxicity
Head & Neck Tumors	Administer 840 mg intravenously x 1 dose, then 420 mg intravenously every 21 days thereafter until disease progression or unmanageable toxicity.

VI. Billing Code/Availability Information

HCPCS Code:

- J9306 - Injection, pertuzumab, 1 mg; 1 mg = 1 billable unit

NDC:

- Perjeta 420 mg/14 mL solution for injection: 50242-0145-xx

VII. References (STANDARD)

1. Perjeta [package insert]. South San Francisco, CA; Genentech, Inc.; February 2021. Accessed March 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) pertuzumab. National Comprehensive Cancer Network, 2021. 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 March 2021.
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer Version 3.2021. National Comprehensive Cancer Network, 2021. 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 NCCN Guidelines, go online to NCCN.org. Accessed March 2021.
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10. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer, Version 2.2021. National Comprehensive Cancer Network, 2021. 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 NCCN Guidelines, go online to NCCN.org. Accessed March 2021.
11. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer 1.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.
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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
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

ICD-10	ICD-10 Description
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 male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola , unspecified male 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

ICD-10	ICD-10 Description
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
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
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
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 Determinations (LCDs), and Local Coverage Articles (LCAs) 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/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 (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

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

HER2-Positive Breast Cancer

Neoadjuvant treatment							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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	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).

				docetaxel (T) +HP FEC followed by THP			
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 survival benefits. • 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	DFS	Adjuvant HER2-positive, node-positive or high-risk node-negative High risk: <35 years; tumor > 2cm, ER/PR-	• 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.

				AC-T + trastuzumab (H)		negative, tumor grade 2 or 3	
First-Line Therapy in Recurrent or Metastatic HER2-Positive Breast Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pertuzumab+ trastuzumab + docetaxel	1 preferred	Yes	Phase 3 (CLEOPATRA), randomized, double-blind, placebo-controlled Second interim analysis	Docetaxel + trastuzumab+ placebo	PFS	First-line in metastatic breast cancer (patients with prior adjuvant or neoadjuvant therapy, with or without 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)	• Pertuzumab group significantly prolonged PFS and OS.
Pertuzumab+ trastuzumab + paclitaxel	2A preferred	No	Phase 2 Follow up analysis	N/A	PFS	First- or second-line in metastatic breast cancer	• Pertuzumab+ trastuzumab +paclitaxel is associated with a favorable OS and PFS and offers an alternative to docetaxel-based therapy.

Trastuzumab+ paclitaxel	2A other	Yes	Phase 3, randomized, multicenter	Trastuzumab+ paclitaxel + carboplatin	ORR	First-line for metastatic disease (taxane not used in neoadjuvant or adjuvant therapy)	• Trastuzumab+ paclitaxel + carboplatin improved ORR and PFS. • Trend toward improved OS with trastuzumab+ paclitaxel + carboplatin however, not statistically significant. • Increased rates of neutropenia was associated with TPC.
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.
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 (MARIANNE), randomized	(Docetaxel or paclitaxel)+ trastuzumab vs T-DM1 + pertuzumab (T-DM1 + P)	PFS Safety	First-line therapy in locally advanced or metastatic breast cancer with ≥ 6-month treatment-free interval since completion of adjuvant therapy	• No significant difference in PFS was observed between ado-trastuzumab-containing regimens and the control group. • T-DM1 is an effective and tolerable alternative first-line treatment for HER2-positive metastatic breast cancer.

Ado- trastuzumab emtansine (T-DM1)	2A	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.
Second-Line Therapy in Recurrent or Metastatic HER2-Positive Breast Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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	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	• 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.

		completing adjuvant therapy)				for locally advanced or metastatic disease	
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 (TH3RESA), randomized, parallel assessment, open-label	Treatment of physician's choice (TPC)	PFS OS	Third-line therapy or later after at least two HER2-directed regimens in the advanced setting (with progression on both trastuzumab- and lapatinib-containing regimens)	• Patients who had progressed on two or more HER2-directed regimens, T-DM1 treatment resulted in a significant improvement in OS versus TPC.
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	Lapatinib+ capecitabine demonstrated a significant benefit in TTP and a trend

						setting) and prior treatment with an anthracycline and a taxane (metastatic or adjuvant setting)	towards an improvement in OS compared to capecitabine alone.
Trastuzumab+ capecitabine	2A other	No	Phase 3 (TBP), randomized	Capecitabine	TTP	After prior trastuzumab-based therapy (in adjuvant or metastatic setting)	• Continuing trastuzumab and adding capecitabine beyond trastuzumab progression showed a significant improvement in ORR and TTP compared with capecitabine alone. • However, difference in OS was not significant.
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.

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	-----	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 and RAS wild-type	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 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.