Kadcyla® (ado-trastuzumab emtansine)
(Intravenous)

-E-

Document Number: IC-0385

Last Review Date: 05/03/2021
Date of Origin: 01/07/2019
Dates Reviewed: 01/2019, 04/2019, 07/2019, 10/2019, 01/2020, 04/2020, 07/2020, 10/2020, 01/2021, 05/2021

I. Length of Authorization [1]

Coverage will be provided for six months and may be renewed unless otherwise specified.

- Use as adjuvant treatment of HER2-positive disease in patients with locally advanced or early breast cancer with residual disease is limited to 14 cycles (42 weeks total).

II. Dosing Limits

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

- Kadcyla 100 mg vial – 1 vial every 21 days
- Kadcyla 160 mg vial – 3 vials every 21 days

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

- 480 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient 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**
- Used as single agent therapy; **AND**
- Therapy will not be substituted with or for any trastuzumab-based formulation (i.e., trastuzumab [or trastuzumab biosimilar product], fam-trastuzumab deruxtecan-nxki, trastuzumab-hyaluronidase, pertuzumab/trastuzumab and hyaluronidase-zzxf, etc.); **AND**

Breast Cancer † [1,2,3,4,7]

- Used as adjuvant therapy in patients with early breast cancer with residual invasive disease after neoadjuvant taxane and trastuzumab-based therapy; **OR**

- Patient has metastatic or recurrent disease

Non-Small Cell Lung Cancer ‡ [2,5,11]

- Patient has adenocarcinoma histology; **AND**

For metastatic disease:

- Use of ado-trastuzumab emtansine will be restricted to patients with a contraindication or intolerance to fam-trastuzumab deruxtecan-nxki

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)

***HER2-positive overexpression criteria:** [7,8]

- 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+

IV. Renewal Criteria [1,5]

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: hepatotoxicity, pulmonary toxicity (i.e., interstitial lung disease, pneumonitis), thrombocytopenia, neurotoxicity, infusion-related and hypersensitivity reactions, hemorrhage, extravasation at infusion site, etc.; **AND**
- Left ventricular ejection fraction (LVEF) within the previous 3 months as follows:

- Metastatic or Recurrent Breast Cancer: >45% OR LVEF is ≥40% and absolute decrease is <10% from baseline; **OR**
- All other indications: Left ventricular ejection fraction (LVEF) is ≥ 50% OR LVEF is ≥45% and absolute decrease is <10% from baseline; **AND**

- Adjuvant treatment of breast cancer is limited to 14 cycles (42 weeks total)

V. Dosage/Administration [1,5,12]

Indication	Dose
Adjuvant therapy of early stage breast cancer	3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) for up to 14 cycles unless there is disease recurrence or unmanageable toxicity.
Metastatic or recurrent breast cancer, NSCLC	3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9354 - Injection, ado-trastuzumab emtansine, 1 mg; 1 billable unit = 1 mg

NDC:

- Kadcyla 100 mg single-use vial: 50242-0088-xx
- Kadcyla 160 mg single-use vial: 50242-0087-xx

VII. References (STANDARD)

1. Kadcyla [package insert]. South San Francisco, CA; Genentech, Inc; September 2020. Accessed April 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ado-trastuzumab emtansine. 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 April 2021.
3. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012 Nov 8; 367(19):1783-91.
4. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019 Feb 14;380(7):617-628.
5. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial. J Clin Oncolo 2017, 35: Abstract 8510.

6. 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.
7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer 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 Guidelines, go online to NCCN.org. Accessed April 2021.
8. 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.
9. Hematology/Oncology Pharmacy Association (2019). *Intravenous Cancer Drug Waste Issue Brief*. Retrieved from http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.pdf
10. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016 Feb 29;352:i788.
11. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer, Version 4.2021. 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 April 2021.
12. Jhaveri KL, Wang XV, Luoh SW, 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.

VIII. References (ENHANCED)

1e. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012 Jan 12;366(2):109-19. doi: 10.1056/NEJMoa1113216. Epub 2011 Dec 7.
2e. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015 Feb 19;372(8):724-34. doi: 10.1056/NEJMoa1413513.
3e. Datko FM, D'Andrea G, Dickler M, et al. Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with HER2-overexpressing metastatic breast cancer (MBC). Journal of Clinical Oncology 2012 30:27_suppl, 134-134.
4e. Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall

survival and updated progression-free survival results from a phase II study. Breast Cancer Res Treat. 2016 Jul;158(1):91-97. doi: 10.1007/s10549-016-3851-7. Epub 2016 Jun 15.

5e. Robert N1, 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. J Clin Oncol. 2006 Jun 20;24(18):2786-92.

6e. Ellis PA, Barrios CH, Eiermann W, et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. Journal of Clinical Oncology 2015 33:15_suppl, 507-507.

7e. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol. 2017 Jun;18(6):743-754. doi: 10.1016/S1470-2045(17)30313-3. Epub 2017 May 16.

8e. Cameron D, Casey M, Oliva C, et al. 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. doi: 10.1634/theoncologist.2009-0181. Epub 2010 Aug 24.

9e. 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. doi: 10.1200/JCO.2011.35.6725. Epub 2012 Jun 11.

10e. 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.

11e. 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 Mar 1;28(7):1138-44. doi: 10.1200/JCO.2009.24.2024. Epub 2010 Feb 1.

12e. Gatzemeier U, Groth G, Butts C, et al. Randomized phase II trial of gemcitabine–cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. Ann Oncol. 2004 Jan;15(1):19-27.

13e. Mazières J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. 2013 Jun 1;31(16):1997-2003. doi: 10.1200/JCO.2012.45.6095. Epub 2013 Apr 22.

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. doi: 10.1200/JCO.2010.30.8213. Epub 2010 Dec 13.

15e. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer [published correction appears in N Engl J Med. 2017 Aug 17;377(7):702] [published correction appears in N Engl J Med. 2018 Oct 18;379(16):1585]. N Engl J Med. 2017;377(2):122–131.

16e. 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.

17e. 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.

18e. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020 Feb 13;382(7):597-609. doi: 10.1056/NEJMoa1914609. Epub 2019 Dec 11. Erratum in: N Engl J Med.

19e. 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.

20e. Smit EF, Nakagawa K, Nagasaka M, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung01[abstract]. J Clin Oncol 2020;38:Abstract 9504.

21e. 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.

22e. 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.

23e. 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.

24e. Magellan Health, Magellan Rx Management. Kadcyla Clinical Literature Review Analysis. Last updated April 2021. Accessed April 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung

C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
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
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
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

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

Appendix 3 – CLINICAL LITERATURE REVIEW

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

HER2-Positive Breast Cancer

Adjuvant therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ado-trastuzumab emtansine (14 cycles)	1 preferred if residual disease after pre-operative therapy	Yes if residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment	Phase 3 (KATHERINE), randomized, open-label	Trastuzumab (14 cycles)	DFS	Invasive disease after neoadjuvant taxane-containing chemotherapy (with or without anthracyclines) and trastuzumab	• Among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone.
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

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
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)	• The combination of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, when used as first-line treatment for HER2-positive metastatic breast cancer 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
Trastuzumab+ vinorelbine	2A other	No	Phase 3 (HERNATA), randomized	Trastuzumab+ docetaxel	TTP	First-line	• Neither arm demonstrated a significant improve 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 • T-DM1 is an effective and tolerable alternative first-line treatment for HER2-positive 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	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

		or within 6 months of completing adjuvant therapy)					
Second-Line or Subsequent Therapy in 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 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
Ado-trastuzumab emtansine (T-DM1)	2A other	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic disease	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

		or developed disease recurrence during or within 6 months of completing adjuvant therapy)					
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+ 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 • 4.5mon OS advantage with lapatinib+ trastuzumab in patients with pretreated HER2-positive metastatic breast cancer
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	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.

Non-Small Cell Lung Cancer

Adenocarcinoma/Non-squamous

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Ado-trastuzumab emtansine (T-DM1)	2A	No	Phase 2 bucket trial	N/A	ORR	0-4 prior therapies	• Ado-trastuzumab emtansine is active and well tolerated in pts with HER2 mutant lung cancers based on ORR and PFS
Trastuzumab+ gemcitabine+ cisplatin	None	No	Phase 2, randomized	Gemcitabine+ cisplatin	ORR	First-line	• Clinical benefit in addition of trastuzumab was not observed due to small subgroup of patients with HER2-positive disease (only 6 patients)
Afatinib	None	No	Retrospective analysis	N/A	-----	----------	• Study suggested the potential efficacy of HER2-targeted drugs
Fam-trastuzumab deruxtecan-nxki	2A	No	Phase 2 (DESTINY-Lung01)	N/A	ORR	Relapsed or refractory disease or no standard treatment is available	• Fam-trastuzumab deruxtecan-nxki demonstrated an ORR of 61.8% in patients with HER2-mutated NSCLC. Duration of response was not reached after a median follow-up of 8 months.

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 emtansine (TDM-1)	2A certain circumstances	No	Phase 2 (NCI-MATCH)	N/A	ORR	Following at least one line of standard systemic therapy or for whom no standard therapy was available	• Treatment with ado-trastuzumab demonstrated an ORR of 5.6% with 2 out of 3 patients with salivary gland tumors experiencing a partial response.