Perjeta® (pertuzumab)
(Intravenous)

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I. Length of Authorization [1,2]

- Initial: Prior authorization validity will be provided initially for 6 months (180 days).
- Renewal: Prior authorization validity may be renewed every 6 months (180 days), unless otherwise specified.
  - Neoadjuvant and adjuvant treatment in Breast Cancer may be renewed up to a maximum of 1 year of treatment [18 cycles].

II. Dosing Limits

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]

Prior authorization validity is provided in the following conditions:

- Member 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**
- Member has human epidermal growth factor receptor 2 (HER2)-positive* disease as determined by an FDA-approved or Clinical Laboratory Improvement Amendments (CLIA)-compliant test❖; **AND**
- Therapy will not be used in combination with pertuzumab/trastuzumab and hyaluronidase-zzxf (Phesgo); **AND**

Breast Cancer † ‡ [1-3,5-8,13,19,12e-15e,24e-26e]

- Used as neoadjuvant or preoperative therapy; **AND**

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- Member has ≥ T1c disease, node positive disease, or inflammatory disease; **AND**
- Used in combination with trastuzumab and a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.); **OR**

- Used as adjuvant therapy; **AND**
  - Member has ≥ T1 disease, node positive disease, or inflammatory disease (unless otherwise specified); **AND**
    - Used in combination with trastuzumab and chemotherapy (pN+ ONLY); **OR**
    - Used in combination with trastuzumab (pN+ ONLY); **OR**
  - Used after completion of planned chemotherapy and following mastectomy or breast-conserving surgery; **AND**
    - Member has ≥ ypT0N0 or pCR disease by axillary staging; **AND**
    - Used in combination with trastuzumab; **AND**
    - Member has node positive disease at initial staging; **OR**
- Used for recurrent unresectable (local or regional) or metastatic disease OR inflammatory breast cancer with no response to preoperative systemic therapy; **AND**
  - Used in combination with one of the following:
    - Trastuzumab and aromatase inhibition, with or without palbociclib as first-line maintenance therapy in members who initiated treatment with chemotherapy, pertuzumab, and trastuzumab, and the chemotherapy was stopped; **AND**
      - Member has hormone receptor-positive disease; **AND**
        - Member is postmenopausal; **OR**
        - Member is premenopausal and is treated with ovarian ablation/suppression; **OR**
        - Member is a male (sex assigned at birth) **¥**
    - Trastuzumab and a taxane (e.g., docetaxel, paclitaxel) as first-line therapy
    - Trastuzumab with or without cytotoxic therapy as subsequent therapy in members previously treated with chemotherapy and trastuzumab (without pertuzumab); **AND**

Fourth-line therapy and beyond ONLY:
➢ Patient must demonstrate an inadequate response to one of the following regimens, unless there is a contraindication or intolerance, prior to approval of pertuzumab: – Lapatinib/capecitabine – Trastuzumab/lapatinib

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- Trastuzumab/generically available agent(s) (e.g., trastuzumab/capecitabine, etc. [*see NCCN Breast Cancer guidelines for complete list of alternative regimens*])

- Fam-trastuzumab deruxtecan as first-line therapy

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

Central Nervous System (CNS) Cancers ‡ [2,18,36e]

- Member has brain metastases from breast cancer; **AND**
- Used in combination with trastuzumab; **AND**
- Patient must demonstrate an inadequate response to capecitabine/lapatinib, unless there is a contraindication or intolerance, prior to approval of pertuzumab

Colorectal Cancer (CRC) λ ‡ [2,9-12,16e]

- Used for RAS and BRAF wild-type (WT) disease in combination with trastuzumab; **AND**
  - Used as initial treatment for unresectable metastatic disease and previous FOLFOX or CapeOX within the past 12 months; **OR**
  - Used as subsequent therapy for progression of advanced or metastatic disease; **AND**
    - Member has not previously received HER2-targeted therapy

λ *Note: NCCN recommends universal MMR or MSI testing in all newly diagnosed members. If deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., TMB>50 mut/Mb), treatment should include checkpoint inhibitor immunotherapy if the member is a candidate.*

Head and Neck Cancers ‡ [2,14,15,20e]

- Member has salivary gland tumors; **AND**
- Used in combination with trastuzumab; **AND**
- Member has recurrent disease with one of the following:
  - Distant metastases
  - Unresectable locoregional recurrence with prior radiation therapy (RT)
  - Unresectable second primary with prior RT; **AND**
- Patient must demonstrate an inadequate response to trastuzumab/docetaxel, unless there is a contraindication or intolerance, prior to approval of pertuzumab

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Biliary Tract Cancers (Gallbladder Cancer or Intra-/Extra-Hepatic Cholangiocarcinoma) ‡ [2,16,17]

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

Appendiceal Neoplasms and Cancers ‡ [2,21]

- Member has RAS and BRAF wild-type (WT) disease; **AND**
- Used in combination with trastuzumab; **AND**
- Used as subsequent therapy (if not previously given) for recurrent, progressive, metastatic peritoneal-only, or extraperitoneal disease

Small Bowel Adenocarcinoma ‡ [2,22]

- Member has RAS and BRAF wild-type (WT) disease; **AND**
- Used in combination with trastuzumab; **AND**
- Used as subsequent therapy for advanced or metastatic disease (if not previously given)

***HER2-positive overexpression criteria:**
Breast, CNS, and Head and Neck: [3,4]

• Immunohistochemistry (IHC) assay 3+; **OR**
• Dual-probe in situ hybridization (ISH) assay HER2 *(ERBB2)*/CEP17 ratio ≥ 2.0 AND average HER2 *(ERBB2)* copy number ≥ 4.0 signals/cell; **OR**
• Dual-probe in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following:
  ○ HER2 *(ERBB2)*/CEP17 ratio ≥ 2.0 AND average HER2 *(ERBB2)* copy number < 4.0 signals/cell AND concurrent IHC 3+; **OR**
  ○ HER2 *(ERBB2)*/CEP17 ratio < 2.0 AND average HER2 *(ERBB2)* copy number ≥ 6.0 signals/cell AND concurrent IHC 2+ or 3+; **OR**
  ○ HER2 *(ERBB2)*/CEP17 ratio < 2.0 AND average HER2 *(ERBB2)* copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent IHC 3+

Colorectal Cancer and Appendiceal Neoplasms and Cancers, and Small Bowel Adenocarcinoma: [10,11,21,22]
• Immunohistochemistry (IHC) assay 3+; **OR** • Fluorescence in situ hybridization (FISH) HER2 *(ERBB2)*/CEP17 ratio ≥ 2 AND concurrent IHC 2+; **OR**

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• Next-generation sequencing (NGS) panel HER2 *(ERBB2)* amplification
Biliary Tract Cancer: [17]

• Immunohistochemistry (IHC) assay 3+; **OR**
• Dual-probe in situ hybridization (ISH) assay HER2 *(ERBB2)*/CEP17 ratio ≥ 2.0 AND average HER2 *(ERBB2)* copy number ≥ 4.0 signals/cell; **OR**
• Dual-probe in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following:
  ○ HER2 *(ERBB2)*/CEP17 ratio ≥ 2.0 AND average HER2 *(ERBB2)* copy number < 4.0 signals/cell AND concurrent IHC 3+; **OR**
  ○ HER2 *(ERBB2)*/CEP17 ratio < 2.0 AND average HER2 *(ERBB2)* copy number ≥ 6.0 signals/cell AND concurrent IHC 2+ or 3+; **OR**
  ○ HER2 *(ERBB2)*/CEP17 ratio < 2.0 AND average HER2 *(ERBB2)* copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent IHC 3+; **OR**
• Next-generation sequencing (NGS) panel HER2 amplification

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

Enhanced Oncology Value (EOV) Program – Redacted indications
Uses not listed above have inadequate data to support efficacy and are excluded from prior authorization validity. Other treatment options including, but are not limited to, the following may be appropriate: radiation therapy, surgery, traditional chemotherapy (e.g., platinum, taxane), compassionate use/expanded access programs, clinical trials, supportive care, integrative and complementary therapies.

❖ *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]

Prior authorization validity may be renewed based upon the following criteria:

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- Member continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Duration of authorization has not been exceeded *(refer to Section I)*; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: left ventricular dysfunction, severe infusion-related reactions, hypersensitivity reactions/anaphylaxis, etc.; **AND**
- Left ventricular ejection fraction (LVEF) obtained within the previous 3 months as follows:
- Neoadjuvant and adjuvant treatment of breast cancer: LVEF is ≥ 50% OR LVEF has had an absolute decrease of < 10% from baseline
- All other indications: LVEF is > 45% OR LVEF is 40% to 45% and absolute decrease is < 10% from baseline

V. Dosage/Administration [1-3,10-13,15,16,18,20]

Indication	Dose
Breast Cancer	**Initial Dose** Administer 840 mg intravenously x 1 dose **Maintenance Dose** Administer 420 mg intravenously every 21 days thereafter until disease progression or unmanageable toxicity (unless otherwise specified below). • Neoadjuvant/preoperative therapy consists of 3 to 9 cycles prior to surgery. • Use for neoadjuvant/preoperative and adjuvant treatment is limited to a total of 1 year of treatment (total of 18 cycles).
All other indications	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 billable unit = 1 mg

NDC:

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

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VII. References (STANDARD)

1. Perjeta [package insert]. South San Francisco, CA; Genentech, Inc.; April 2026. Accessed May 2026.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) pertuzumab. National Comprehensive Cancer Network, 2026. 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 May 2026.
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer, Version 2.2026. National Comprehensive Cancer Network, 2026. 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 May 2026.
4. 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.
5. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016 Jun;17(6):791-800. doi: 10.1016/S1470-2045(16)00163-7. Epub 2016 May 11.
6. Baselga J, Cortes J, Kim SB, et al. CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-119.
7. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013 Sep;24(9):2278-84.
8. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377(2):122-131.
9. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. Clin Oncol. 2018 Feb 20;36(6):536-542.
10. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer, Version 2.2026. National Comprehensive Cancer Network, 2026. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most

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recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed May 2026.

11. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer, Version 2.2026. National Comprehensive Cancer Network, 2026. 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 May 2026.
12. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2019;20(4):518-530. doi:10.1016/S1470-2045(18)30904-5.
13. Swain SM, Ewer MS, Viale G, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol. 2018;29(3):646-653. doi:10.1093/annonc/mdx773.
14. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancer, Version 1.2026. National Comprehensive Cancer Network, 2026. 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 May 2026.
15. Kurzrock R, Bowles DW, Kang H, et al. Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: results from MyPathway, a phase Iia multiple basket study. Ann Oncol. 2020;31(3):412-421.
16. Javle M, Borad MJ, Azad NS, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2021 Sep;22(9):1290-1300. Doi: 10.1016/S1470-2045(21)00336-3. Epub 2021 Jul 30.
17. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Biliary Tract Cancers, Version 1.2026. National Comprehensive Cancer Network, 2026. 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 May 2026.
18. Lin NU, Pegram M, Sahebjam S, et al. Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary

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Analysis of a Phase II Study. J Clin Oncol. 2021 Aug 20;39(24):2667-2675. doi: 10.1200/JCO.20.02822.

19. Tolaney SM, Jiang Z, Zhang Q, et al; DESTINY-Breast09 Trial Investigators. Trastuzumab Deruxtecan plus Pertuzumab for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2025 Oct 29. doi: 10.1056/NEJMoa2508668. Epub ahead of print. PMID: 41160818.
20. Mette S van Ramshorst, Anna van der Voort, Erik D van Werkhoven, et al; Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial, The Lancet Oncology, Volume 19, Issue 12, 2018, Pages 1630-1640, ISSN 1470-2045, https://doi.org/10.1016/S1470-2045(18)30570-9.
21. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Appendiceal Neoplasms and Cancers, Version 2.2026. National Comprehensive Cancer Network, 2026. 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 May 2026.
22. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Bowel Adenocarcinoma, Version 2.2026. National Comprehensive Cancer Network, 2026. 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 May 2026.

VIII. References (ENHANCED)

1e. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366(2):109-119.
2e. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011 Sep 1;29(25):3366-73. doi: 10.1200/JCO.2011.35.0868. Epub 2011 Jul 18.
3e. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-83. doi: 10.1056/NEJMoa0910383.
4e. 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.

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5e. 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.

6e. 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.

7e. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol. 2006 Jun 20;24(18):2786-92.

8e. 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.

9e. 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.

10e. 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. doi: 10.1056/NEJMoa1209124. Epub 2012 Oct 1.

11e. 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.

12e. 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.

13e. 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.

14e. 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.

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15e. 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.

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

17e. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer [published correction appears in N Engl J Med. 2020 Feb 6;382(6):586]. N Engl J Med. 2020;382(7):597-609. doi:10.1056/NEJMoa1914609.

18e. 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.

19e. 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.

20e. 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.

21e. Jhaveri KL, Wang XV, Makker V, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. Ann Oncol. 2019 Nov 1;30(11):1821-1830. doi: 10.1093/annonc/mdz291.

22e. Saura C, Oliveira M, Feng YH, et al. NALA Investigators. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol. 2020 Sep 20;38(27):3138-3149. doi: 10.1200/JCO.20.00147. Epub 2020 Jul 17.

23e. Rugo HS, Im SA, Cardoso F,et al. SOPHIA Study Group. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021 Apr 1;7(4):573-584. doi: 10.1001/jamaoncol.2020.7932.

24e. Taghian A. and Merajver S. (Oct 2022). Inflammatory breast cancer: Clinical features and treatment. In Hayes DF, Pierce LJ, Chagpar AB, et al. (Eds.), UptoDate. Accessed September 2023. Available from: https://www.uptodate.com/contents/inflammatory-breast-cancer-clinical-features-and-treatment?search=inflammatory%20breast%20cancer&source=search_result&selectedTitle=1~48&usage_type=default&display_rank=1#H4025803376.

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25e. Sikov W.M. (July 2023). Neoadjuvant therapy for patients with HER2-positive breast cancer. In Burstein HJ, Vora SR (Eds.), UptoDate. Accessed September 2023. Available from: https://www.uptodate.com/contents/neoadjuvant-therapy-for-patients-with-her2-positive-breast-cancer?sectionName=TIMING%20OF%20HER2-DIRECTED%20AGENTS&search=inflammatory%20breast%20cancer%20treatment&topicRef=768&anchor=H1845125338&source=see_link#H1845125338.

26e. Burstein HJ (Apr 2023). Adjuvant systemic therapy for HER2-positive breast cancer. In Isaacs C and Vora SR. (Eds.), UptoDate. Accessed September 2023. Available from: https://www.uptodate.com/contents/adjuvant-systemic-therapy-for-her2-positive-breast-cancer?sectionName=Non-anthracycline-based%20therapy&search=inflammatory%20breast%20cancer&topicRef=106774&anchor=H1352264107&source=see_link#H1237051481.

27e. Siena S, Di Bartolomeo M, Raghav KPS, et al. A phase II, multicenter, open-label study of trastuzumab deruxtecan in patients with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01. J Clin Oncol 2020;38(suppl; abstr 4000).

28e. Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and Trastuzumab in Heavily Pretreated Metastatic Breast Cancer. J Clin Oncol 2007;25:3853-3858.

29e. Lee YR, Huh SJ, Lee DH, et al. Phase II Study of Vinorelbine Plus Trastuzumab in HER2 Overexpressing Metastatic Breast Cancer Pretreated with Anthracyclines and Taxanes. J Breast Cancer. 2011;14(2):140-146. doi:10.4048/jbc.2011.14.2.140.

30e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers, Version 1.2026. National Comprehensive Cancer Network, 2026. 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 May 2026.

31e. Strickler JH, Cercek A, Siena S, et al. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study. Lancet Oncol. 2023 May; 24(5): 496-508. doi.org/10.1016/S1470-2045(23)00150-X.

32e. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017;377:523-533.

33e. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med 2018;379:753-763.

34e. Piccart M, Procter M, Fumagalli D, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY

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Trial: 6 Years' Follow-Up. J Clin Oncol. 2021 May 1;39(13):1448-1457. doi: 10.1200/JCO.20.01204.

35e. 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.

36e. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013 Jan;14(1):64-71.

37e. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial☆. Ann Oncol. 2020 Oct;31(10):1350-1358.

38e. 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.

39e. Freedman RA, Gelman RS, Anders CK, et al; Translational Breast Cancer Research Consortium. TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. J Clin Oncol. 2019 May 1;37(13):1081-1089.

40e. Jerusalem G, Park YH, Yamashita T, et al. Trastuzumab Deruxtecan in HER2-Positive Metastatic Breast Cancer Patients with Brain Metastases: A DESTINY-Breast01 Subgroup Analysis. Cancer Discov. 2022 Dec 2;12(12):2754-2762.

41e. Press MF, Sauter G, Buyse M, et al. HER2 Gene Amplification Testing by Fluorescent In Situ Hybridization (FISH): Comparison of the ASCO-College of American Pathologists Guidelines With FISH Scores Used for Enrollment in Breast Cancer International Research Group Clinical Trials. J Clin Oncol. 2016 Oct 10;34(29):3518-3528. doi: 10.1200/JCO.2016.66.6693. PMID: 27573653; PMCID: PMC5074347.

42e. Loibl S, Jassem J, Sonnenblick A, et al. Adjuvant Pertuzumab and Trastuzumab in Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in the APHINITY Trial: Third Interim Overall Survival Analysis With Efficacy Update. J Clin Oncol. 2024 Nov;42(31):3643-3651. doi: 10.1200/JCO.23.02505. Epub 2024 Sep 11. PMID: 39259927.

43e. Metzger O, Mandrekar S, Goel S, et al. Palbociclib for Hormone-Receptor-Positive, HER2-Positive Advanced Breast Cancer. N Engl J Med. 2026 Jan 29;394(5):451-462. doi: 10.1056/NEJMoa2511218. PMID: 41604639.

44e. Arpino G, de la Haba Rodríguez J, et al. PERTAIN Study Group. Pertuzumab, Trastuzumab, and an Aromatase Inhibitor for HER2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer: PERTAIN Final Analysis. Clin Cancer Res. 2023 Apr 14;29(8):1468-1476. doi: 10.1158/1078-0432.CCR-22-1092. PMID: 36716289; PMCID: PMC10102835.

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45e. Gupta R, Meric-Bernstam F, et al. Pertuzumab Plus Trastuzumab in Patients With Colorectal Cancer With ERBB2 Amplification or ERBB2/3 Mutations: Results From the TAPUR Study. JCO Precis Oncol. 2022 Oct;6:e2200306. doi: 10.1200/PO.22.00306. PMID: 36315917.
46e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Bowel Adenocarcinoma, Version 2.2026. National Comprehensive Cancer Network, 2026. 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 May 2026.
47e. Liu D, Makker V, Buonocore D, et al. Final analysis of multi-histology basket trial expansion of ado-trastuzumab emtansine in patients with HER2 amplified cancers. J Clin Oncol. 2023;41(16_suppl):3025
48e. Prime Therapeutics Management. Perjeta Clinical Literature Review Analysis. Last updated May 2026. Accessed May 2026.

Appendix A – Non-Quantitative Treatment Limitations (NQTL) Factor Checklist

Non-quantitative treatment limitations (NQTLs) refer to the methods, guidelines, standards of evidence, or other conditions that can restrict how long or to what extent benefits are provided under a health plan. These may include things like utilization review or prior authorization. The utilization management NQTL applies comparably, and not more stringently, to mental health/substance use disorder (MH/SUD) Medical Benefit Prescription Drugs and medical/surgical (M/S) Medical Benefit Prescription Drugs. The table below lists the factors that were considered in designing and applying prior authorization to this drug/drug group, and a summary of the conclusions that Prime's assessment led to for each.

Factor	Conclusion
Indication	Yes: Consider for PA
Safety and efficacy	Yes: Consider for PA
Potential for misuse/abuse	No: PA not a priority
Cost of drug	Yes: Consider for PA

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

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ICD-10	ICD-10 Description
C08.1	Malignant neoplasm of sublingual gland
C08.9	Malignant neoplasm of major salivary gland, unspecified
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
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
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C50.011	Malignant neoplasm of nipple and areola, right female breast
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

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ICD-10	ICD-10 Description
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

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ICD-10	ICD-10 Description
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
C50.A0	Malignant inflammatory neoplasm of unspecified breast
C50.A1	Malignant inflammatory neoplasm of right breast
C50.A2	Malignant inflammatory neoplasm of left 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
C79.31	Secondary malignant neoplasm of brain
D37.031	Neoplasm of uncertain behavior of the sublingual salivary glands
D37.032	Neoplasm of uncertain behavior of the submandibular salivary glands
D37.039	Neoplasm of uncertain behavior of the submandibular salivary glands
D37.3	Neoplasm of uncertain behavior of appendix
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

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

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

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

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdictio	**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
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
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

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