Redefining Treatment Across the Spectrum of HR+/HER2-Expressing Metastatic Breast Cancer

A SHARED DECISION-MAKING POCKET REFERENCE GUIDE

Importance of Molecular Testing and Patient Counseling[1,2]

- Histopathologic and molecular features of breast cancer can guide treatment selection
- HER2 status is a key treatment selection driver, and expression varies widely
  - Often evaluated with immunohistochemistry (IHC) and molecular analysis with fluorescence in situ hybridization (FISH)
  - Tumors may not be characterized accurately based on conventional testing, particularly with lower degrees of HER2 expression/amplification; new assays and testing approaches may help to optimize tumor characterization and treatment selection

Tactics for Weighing the Risks and Benefits of Therapy Selection[3,4]

- Patient-centered communication is essential to balance risks and benefits of therapy
- Improving patient knowledge of key treatment aspects, understanding patient cognitive and emotional needs, and implementing shared-decision making can be beneficial when selecting treatment options
- Agency for Healthcare Research and Quality SHARE Approach:
  - Seeking out the participation of the patient
  - Helping the patient to explore and compare therapeutic options
  - Assessment of patient preferences and values
  - Reaching a decision with the patient, and
  - Evaluating the decision of the patient

Glossary of Key Terms

ADC	Antibody-drug conjugate: A cancer treatment consisting of a target-specific monoclonal antibody linked to a cytotoxic molecule payload[16]
IHC	Immunohistochemistry: Method of detecting HER2 expression through protein-binding monoclonal or polyclonal antibodies[17]
FISH	Fluorescence in situ hybridization: Method of evaluating HER2 gene amplification using fluorescence microscopy in which DNA probes are created, labeled, and hybridized to target tissue[17]
HER2	Human epidermal growth factor receptor 2: Membrane tyrosine kinase and oncogene that is amplified/overexpressed in approximately 1 in 5 breast cancer cases[17]
HER2-low	Human epidermal growth factor receptor 2-low: A potential new nomenclature for breast cancer that has been characterized in the medical literature as IHC 1+ or 2+ with negative ISH[18]
HER2-ultra low	Human epidermal growth factor receptor 2-ultra low: A potential new nomenclature for breast cancer that has been characterized in the medical literature as IHC 0 with faint, partial membrane staining in ≤10% of tumor cells[12]
HER2-positive	Human epidermal growth factor receptor 2-positive: A subtype of breast cancer marked by HER2 overexpression on IHC evaluation (3+) and/or gene amplification on an in situ hybridization assay on at least one tumor sample. For patients with an IHC 2+ score, reflex ISH testing is required to define HER2 status.[1]

Overview of FDA-Approved ADCs in Metastatic Breast Cancer to Help Facilitate Discussion and Collaborative Decision-Making

ADC	mBC Indications for Adult Patients[5-8]	NCCN Guideline Statements[9]	Key Trial Results
Trastuzumab deruxtecan (T-DXd)	Unresectable or metastatic HER2+ BC treated with a prior anti-HER2-based regimen in the metastatic setting or in the neoadjuvant or adjuvant setting with disease recurrence during or within 6 months of completing therapy. Unresectable or metastatic HER2-low BC treated with prior chemotherapy in the metastatic setting or in the adjuvant setting with disease recurrence during or within 6 months of completing therapy. Unresectable or metastatic HR+, HER2-low or HER2-ultralow BC that has progressed on one or more endocrine therapies in the metastatic setting.	First line: HR+, no germline *BRCA1/2* mutation, and/or HER2 IHC 0+, 1+, or 2+/ISH- unresectable or stage IV disease Second line: HR+/- and HER2+ unresectable or stage IV disease, as well as HR+ and HER2 IHC 0+, 1+, or 2+/ISH- unresectable or stage IV disease (Category 1, preferred) Second line: no germline *BRCA1/2* mutation and HER2 IHC 0+, 1+, or 2+/ISH- unresectable or stage IV TNBC (Category 1, preferred)	**HER2+** DESTINY-Breast 03[10] Improved ORR and PFS in patients pretreated with trastuzumab + taxane vs. T-DM1 **HER2-low** DESTINY-Breast 04[11] Improved ORR, PFS, and OS vs. PC **HER2-low/HER2-ultra low** DESTINY-Breast 06[12] Improved ORR and PFS vs. PC
Trastuzumab emtansine (T-DM1)	HER2+ mBC treated previously with trastuzumab and a taxane, separately or in combination; patients should have received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.	Third-line and beyond: HR+/- and HER2+ unresectable or stage IV disease; if not a candidate for T-DXd, T-DM1 could be considered in the second-line	EMILIA[13] Improved PFS and OS relative to lapatinib + capecitabine with less toxicity in patients with HER2+ advanced BC
Datopotamab deruxtecan (Dato-DXd)	Unresectable or metastatic HR+/HER2- BC with prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.	Second-line: HR+ and HER2 IHC 0, 1+, or 2+/ISH- unresectable or stage IV disease who are not candidates for T-DXd	TROPION-Breast01[14] Improved PFS and ORR vs. ICC
Sacituzumab govitecan (SG)	Unresectable la/metastatic TNBC treated with ≥2 prior systemic therapies, at least 1 for metastatic disease. HR+/HER2- (IHC 0, IHC 1+ or IHC 2+/ISH-) la/mBC treated with endocrine based therapy and ≥2 additional systemic therapies in the metastatic setting.	Second-line: HR+ and HER2- unresectable or stage IV disease who are not candidates for T-DXd (Category 1, preferred) Second-line: unresectable or stage IV TNBC (Category 1, preferred)	TROPiCS-02 Subgroup analysis in HER2-low[15] Patients with HER2-low, HR+ BC receiving SG had superior median PFS and ORR relative to PC

ADC, antibody-drug conjugate; BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICC, investigator's choice of chemotherapy; IHC, immunohistochemistry; ISH, in situ hybridization; la, locally advanced; mBC, metastatic breast cancer; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PC, physician's choice of treatment; TNBC triple negative breast cancer.

Select ADC-Associated Adverse Events and Management Strategies[5-8]

ADC	Black Box Warnings	Potential Management Approaches
T-DXd	ILD, pneumonitis, and embryo-fetal toxicity	• Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms • Permanently discontinue T-DXd in all patients with grade ≥2 ILD/pneumonitis • Advise patients of the risk and to immediately report symptoms
T-DM1	Hepatotoxicity, cardiac toxicity, and embryo-fetal toxicity	• Monitor hepatic function before starting and before each dose • Modify dosing or permanently discontinue as appropriate • Assess LVEF prior to initiation, and monitor; withhold dosing or discontinue treatment as appropriate
Dato-DXd	No black box warnings	• NA
SG	Neutropenia and diarrhea	• Withhold for ANC <1500/mm^3 or neutropenic fever • Monitor blood cell counts periodically during treatment; G-CSF should be considered for secondary prophylaxis • Immediately start anti-infective treatment for patients with febrile neutropenia • Monitor patients with diarrhea; give fluids/electrolytes as needed; begin workup for infectious causes; initiate loperamide if not infectious • For severe diarrhea, withhold SG until resolved to ≤ grade 1 and lower subsequent doses

ADC, antibody-drug conjugate; ANC, absolute neutrophil count; Dato-DXd, datopotamab deruxtecan; G-CSF, granulocyte colony-stimulating factor; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; NA, not applicable; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Sample Questions for Clinicians to Pose to Patients to Facilitate Shared Decision-Making

- What do you already know and understand about breast cancer?
- Are there any aspects of treatment that you are worried about?
- Are you able to tolerate the treatment we've chosen? If not, why not? How can we provide improved support to enhance your treatment?
- Do you understand the risks and benefits of the different treatment choices we are considering? What else would you like to know about them?
- Are you experiencing any side effects related to your treatment? How has this impacted your lifestyle and quality of life?
- What goals do you have regarding your cancer treatment?

Sample Questions for Patients to Pose to Clinicians to Facilitate Shared Decision-Making[19,20]

- Will you tell me about the risks and benefits of the different treatments that we are talking about?
- How do these treatments work?
- What can I expect from the treatments that we are discussing?
- Is there a treatment option that you prefer, and if so, why?
- Are there any ongoing clinical trials that I might benefit from? If there are, where can I learn more about them?
- If I want to consult another physician or other providers before making a treatment decision, do you have any recommendations?
- What financial burden will these treatment options present to me?

Additional questions to pose to your clinician are available from the NCCN Guidelines for Patients (Metastatic Breast Cancer), pages 54-62. This document is available at: https://nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf

Potential questions to pose to the healthcare team are also available at the Cancer.org website, https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/questions-to-ask-your-doctor-about-breast-cancer.html

References

1. Wolff AC, Hale Hammond ME, 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(20):2105-2122.
2. Fernandez AI, Liu M, Bellizzi A, et al. Examination of low ERBB2 protein expression in breast cancer tissue. *JAMA Oncol*. 2022;8(4):1-4.
3. Hawley ST, Kidwell K, Zahrieh D, et al. Improving patient-centered communication in breast cancer: a study protocol for a multilevel intervention of a shared treatment deliberation system (SharES) within the NCI community oncology research program (NCORP) (Alliance A231901CD). *Trials*. 2023;24(1):16.
4. Agency for Healthcare Research and Quality. The SHARE Approach: A Model for Shared Decision Making: Fact Sheet. Accessed July 22, 2024. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tools/factsheet.html
5. ENHERTU (fam-trastuzumab deruxtecan-nxki). Prescribing Information. Daiichi Sankyo; 2024.
6. KADCYLA (ado-trastuzumab emtansine). Prescribing Information. Genentech, Inc.; 2022.
7. DATROWAY (datopotamab deruxtecan-dlnk). Prescribing Information. Daiichi Sankyo; 2025.
8. TRODELVY (sacituzumab govitecan-hziy). Prescribing Information. Gilead Sciences, Inc.; 2024.
9. Gradishar WJ, Moran MS, Abraham J, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer (Version 1.2025). © 2025 National Comprehensive Cancer Network. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org.
10. Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. 2022;386(12):1143-1154.
11. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20.
12. Curigliano G, Hu X, Dent RA, et al. Trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): Primary results from DESTINY-Breast06 (DB-06). *J Clin Oncol*. 2024;42(Suppl 17):LBA1000.
13. Verma S, Miles S, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367:1783-1791.
14. Bardia A, Jhaveri K, Im S, et al. Datopotamab deruxtecan versus chemotherapy in previously treated inoperable/metastatic hormone receptor-positive human epidermal growth factor receptor 2-negative breast cancer: Primary results from TROPION-Breast01. *J Clin Oncol*. 2025;43(3):285-296.
15. Schmid P, Cortés J, Marmé F, et al. Sacituzumab govitecan (SG) efficacy in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer (MBC) by HER2 immunohistochemistry (IHC) status in the phase 3 TROPiCS-02 study. *Ann Oncol*. 2022;33(Suppl 7):214MO.
16. D'Arienzo A, Verrazzo A, Pagliuca M, et al. Toxicity profile of antibody-drug conjugates in breast cancer: practical considerations. *EClinicalMedicine*. 2023;62:102113.
17. Gutierrez C, Schiff R. HER2: biology, detection, and clinical implications. *Arch Pathol Lab Med*. 2011;135(1):55-62.
18. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol*. 2020;38(17):1951-1962.
19. National Comprehensive Cancer Network. NCCN Guidelines for Patients: Metastatic Breast Cancer. 2024. Accessed July 22, 2024. https://nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf
20. American Society of Clinical Oncology. Breast Cancer: Questions to Ask the Health Care Team. Accessed July 22, 2024. https://www.cancer.net/cancer-types/breast-cancer/questions-ask-health-care-team

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